Group- and individual Internet-based **Mindfulness-Based Cognitive Therapy** for distressed cancer patients

Effectiveness and cost-effectiveness

DONDERS SERIES

Félix René Compen

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Paranimfen
Else M. Bisseling
Manu Compen

en later hoorde ik de vleugels
van ganzen in de hemel
hoorde ik hoe stil en leeg
het aan het worden was

Rutger Kopland - "Onder de appelboom"
uit "Onder het vee", 1966

CONTENTS

Chapter 1

General introduction

The number of people living with cancer is increasing

Cancer incidence and mortality are rapidly growing worldwide due to ageing and population growth. This phenomenon is referred to as *double ageing:* people both live longer and the relative proportion of people aged 65 and over increases.[1] Moreover, changes in the prevalence and distribution of the main risk factors for cancer are expected.[2] It is predicted that the incidence of all-cancer cases will increase from 12.7 million new cases in 2008 to 22.2 million by 2030.[3]

Cancer patients suffer from psychological distress

It is recommended that all patients with cancer and all cancer survivors are evaluated for symptoms of psychological distress. Psychological distress is defined by the National Comprehensive Cancer Network (NCCN) as "*a multi-factorial unpleasant emotional experience of a psychological (i.e. cognitive, behavioural, emotional), social, and/or spiritual nature that may interfere with the ability to cope effectively with cancer, its physical symptoms, and its treatment. Distress extends along a continuum, ranging from common normal feelings of vulnerability, sadness and fears to problems that can become disabling, such as depression, anxiety, panic, social isolation, and existential and spiritual crisis*".[4]

Thus, psychological distress can be conceptualised both as a dimensional measure ranging on a continuum or as a dichotomous outcome measure in terms of presence or absence of psychiatric disorder.

Several self-report questionnaires are available to measure psychological distress on a dimensional scale.[5] These questionnaires are estimated to take one quarter of the time and cost one third as much as conducting psychiatric assessments by means of a clinical interview.[6] In clinical practice, screening outcomes are often dichotomized by use of cut-offs for clinically relevant levels of psychological distress to screen for presence of psychiatric disorder.[7] One study assessing clinical levels of psychological distress in a large sample of 4496 cancer patients using the Brief Symptom Inventory found clinically levels of psychological distress in 35%.[8] Another study in a multicentre epidemiological sample of 3724 cancer patients with different types of cancer used the Distress Thermometer and found clinically levels of psychological distress in 52%.[9] The authors listed a slight bias towards younger age as one of the possible reasons of higher prevalence. In all, prevalence estimates of clinically significant levels of psychological distress as measured by self-report screening measures seem to vary somewhere between one third and one out of two cancer patients.

Differences in abovementioned psychological distress prevalence estimates are for a large part caused by different questionnaires used to screen for psychological distress.[9]

Moreover, demographic and clinical variables such as younger age [10, 11] and advanced stage of disease [9] are known to be associated with higher levels of psychological distress. The association between younger age and higher levels psychological distress also implies that the number of distressed cancer patients is not expected to increase proportionally with the increase in people living with cancer mentioned above, as the prevalence of patients living with cancer is expected to increase because of an ageing population.

Outcomes of screening for psychological distress can be used as needs assessment and as a source of information to determine whether referral to psychological or psychiatric services is necessary.[4] However, screening alone is not enough: it is suggested that the one-dimensional concern with intensity of distress should be broadened to include more information about the context of the distress.[5] Positive screens for psychological distress warrant follow-up with further assessment of specific needs and appropriate referral and treatment.[12] Not all distressed cancer patients wish for psychological treatment: some patients might for example have sufficient support from family and friends or prefer not to talk about their problems.[13] What responses should follow a positive screen, remains a topic of research in itself.[5]

In contrast, determining presence or absence of psychiatric disorder by psychiatric assessment in a clinical interview is still considered to be gold standard in terms of prognostic value, as a means of contextual assessment of functional impairments and as needs assessment for additional psychiatric or psychological treatment in cancer patients in general.[9] In a meta-analysis of 94 studies with almost 15000 participants in oncological, haematological and palliative-care settings it was concluded that some combination of mood disorders occurs in 30–40% of cancer patients. Combination diagnoses were common: all types of depression occurred in 21% of patients, depression or adjustment disorder in 32%, and any mood disorder in 38%. There was no significant difference in prevalence between palliative-care and non-palliative-care settings.[14]

Whether or not cancer patients suffer from a higher level of psychological distress or psychiatric disorder compared to healthy controls on the long term is unclear. In a systematic review and meta-analysis of depression and anxiety in long-term cancer survivors compared with spouses and healthy controls it was found that after 2 years or more, cancer patients had much the same prevalence of depression as did spouses and healthy controls (12 vs. 10%). However, the prevalence of anxiety was higher in cancer patients than in healthy controls (18 vs. 14%). This suggests that anxiety, rather than depression, is most likely to be a problem in long-term cancer survivors and spouses compared with healthy controls.[15]

Consequences of psychological distress in cancer are profound

On the shorter term, addressing the psychological distress of cancer patients is important because it has profound consequences for the individual patient and for society as a whole. Psychological co-morbidity in cancer is associated with reduced quality of life, decreased compliance with medical care, prolonged duration of hospital stay and increased (inappropriate) healthcare use.[16-18] For example, it was previously demonstrated that psychological distress was associated with increased use of outpatient and inpatient hospital healthcare, emergency healthcare and prescription medication in a large cross-sectional sample of 4326 heterogeneous-cancer survivors.[18] Providing psychosocial care to cancer patients may thus lead to cost savings in the long-term as cancer patients benefitting from psychosocial care make less use of other healthcare services.[19] This phenomenon is referred to as *cost-offset*: increased mental well-being is supposed to lead to increased adherence with anticancer treatment and supportive lifestyle changes (for example to quit smoking). In addition, productivity losses among the working cancer population may be reduced.[19]

Improved cancer survival rates: the emergence of psycho-oncology

The need for psychological treatment for cancer patients might seem self-evident nowadays, although the recognition of psychological needs of cancer patients by the establishment of psychosocial oncology as a dedicated sub-discipline of oncology is a relatively recent development.[20] The increased recognition of psychological needs of the cancer patient is perhaps best understood within the context of drastically improved survival rates for cancer patients.[20]

In the 1800s, effective treatments for cancer patients were not available. By the mid-19th century the establishment of anaesthesia led to first attempts to remove tumours. Early in the 20th century the possibility of cure emerged with further innovations, the role of radiotherapy as a treatment for cancer opened up hopes for cure, or at least extended life expectancy, later followed by chemotherapy as another alternative and, more recently, targeted therapies.[20] As a result, cancer survival rates drastically improved. In England and Wales, the overall index of net survival increased substantially during the 40-year period of 1971-2011. For patients diagnosed in 1971-72, the index of net survival was 50% at 1 year after diagnosis. Forty years later, the same value of 50% was predicted at 10 years after diagnosis.[21] Progress has been most rapid for hematopoietic and lymphoid malignancies due to improvements in treatment protocols. For example, comparing patients diagnosed in the mid-1970s with those diagnosed during 2006 to 2012, the 5-year relative survival rate has increased from 41% to 71% for acute lymphocytic leukaemia and from 22% to 66% for chronic myeloid leukaemia.[22]

In the 1950s, the first studies on psychological reactions to cancer began to emerge. New psychiatric units at Memorial Sloan-Kettering Cancer Center in New York and Massachusetts General Hospital in Boston were established.

Subsequently, patient advocacy groups in the 1960s and 1970s placed the cancer agenda into the public arena.[20] With more people living longer with the consequences of cancer, cancer survivorship in terms of psychological well-being and quality of life has received an increasing amount of attention.[23] In 2013 the NCCN released guidelines for the provision of general survivorship care and management of long-term or late effects of cancer that survivors might experience, with screening for psychological morbidities and psychiatric assessment.[24]

Although the need for regaining psychological well-being increased with the growing length of cancer survivorship, attention for quality of life and well-being in cancer patients lagged behind due to a predominantly technologically based focus on fighting the disease. As a consequence, mental health professionals began to advocate for: *"The need for person-oriented medicine and the importance of clinical skills involving knowing and understanding the patient in front of you as a person, not a collection of cells, and doing this well enough to have insight into their problems, concerns, and emotions"*[20, 23], for example through founding professional societies (the British Psychosocial Oncology Society in 1982, and the American Psycho-Oncology Society and International Psycho-Oncology Society in 1984).[25]

Evidence-based psychological treatments for cancer patients

In the past 30 years evidence-based psychological treatments for cancer patients increasingly became available. In a meta-analysis of 198 studies including 22238 cancer patients small-to-medium effects of psycho-oncological interventions on emotional distress, anxiety, depression, and health-related quality-of-life (QoL) were found. These effects were mostly sustained in the medium term and even long term.[26]

But does psycho-oncological treatment also provide value for money? In a healthcare system with increasingly scarce resources, data on the cost-effectiveness of psychological treatments is ever more important. In cost-effectiveness studies, the difference in total costs between alternative interventions are weighted against the differences in effectiveness, often expressed as improvement in quality-adjusted life-year (QALY). The QALY is a composite outcome multiplying the life expectancy by the quality of these remaining life-years.[27] A review of 11 cost-effectiveness studies of psycho-oncological interventions including collaborative care interventions (n=4), group interventions (n=4), individual psychological support (n=2), and individual psycho-education (n=1)

concluded that psycho-oncological care is likely to be cost-effective depending on how much society is willing to pay for gain in QALYs in cancer patients.[28] Moreover, since psychological distress levels are higher in people of young age [9] who still have a whole working life in front of them, there is great potential economical impact of early and effective psychological interventions in terms of reducing productivity losses for many years to come.

Despite established effectiveness and cost-effectiveness, evidence-based psychological treatments are not always accessible for cancer patients due to known patient-reported barriers to engaging in face-to-face psychological treatment, stigma, reluctance to return to the hospital, and indirect costs such as travel- and time investment.[29] Therefore, these interventions are increasingly delivered via Internet. Internet-based interventions are easily accessible, save travelling time and can be as effective as their face-to-face counterparts.[30, 31]

Of all evidence-based psychological treatments in psycho-oncology, weaker evidence exists for counselling, support-based and narrative therapy interventions.[32] The strongest evidence base for new psychological intervention research in cancer consists for cognitive behavioural therapy (CBT) and mindfulness-based interventions (MBIs).[32]

Cognitive behavioural therapy

Cognitive behavioural therapy (CBT) has been considered the gold-standard of treatment for psychopathology in general[33] and for psychopathology in cancer patients in particular.[32] CBT focuses on identifying and challenging irrational negative automatic thoughts in order to change them into more realistic or helpful ones. It also aims at altering maladaptive behaviour.[34] The quality of evidence for CBT interventions had improved over the years.[35] A 2015 Cochrane review focusing on psychological interventions in non-metastatic breast cancer patients including 24 RCTs on CBT concluded that women who received CBT showed important reductions in anxiety, depression and mood disturbance.[36] Other studies indicate effectiveness of CBT compared to patient education in reducing psychological distress with small to medium effect sizes in other tumour types e.g. gynaecological[37] and head/neck cancers.[38] Although this evidence is promising, much of it derives from trials under 'ideal' conditions. Few pragmatic trials have been conducted, and it remains unclear how well CBT works in 'real world' settings in patients with complex co-morbidity.[32]

Two studies specifically focused on the cost-effectiveness of CBT in cancer patients. One study found (nonsignificant) lower costs in the CBT group compared to the supportive-

experiential group therapy while effectiveness was almost identical.[39] In highly-distressed cancer patients treated with CBT total costs were on average lower and more QALYs were gained than in those offered a nurse-led self-management intervention, although both findings were statistically not significant. In less-distressed patients, lower effect sizes were found.[40]

Moreover, evidence for the efficacy of internet-delivered CBT in cancer patients is accumulating. Guided Internet-based cognitive behavioural therapy has shown to improve generic psychological outcomes with small effect sizes (17-.21) with occasionally larger effects for disease-related impact outcomes (.17-1.11). Internet-based CBT with a longer treatment duration (>6 weeks) led to more consistent effects on depression.[41] Moreover, CBT-based online interventions for cancer survivors without therapist guidance, or unguided interventions, were found effective in reducing psychological distress and fatigue [42-44], improving QoL [43], improving emotional and social functioning [44], and self-efficacy skills.[45] However, it must be noted that adherence to unguided interventions is often lower than intended [46] and evidence for the effectiveness of self-guided interventions in cancer patients is still limited.[47]

Mindfulness-based interventions

In addition to CBT, a minority of intervention research in psycho-oncology has involved mindfulness-based Interventions (MBIs) such as Mindfulness-based Stress Reduction (MBSR) [48] and Mindfulness-based Cognitive Therapy (MBCT).[49] These are increasingly being applied in oncology. Mindfulness is often defined as:*"Paying attention, on purpose, in the present moment and non-judgmentally"*.[48] Whilst CBT focuses on identifying and challenging irrational thoughts and behaviour, many of cancer-related thoughts and cognitions are not irrational. Anxiety for cancer recurrence, once having been treated for cancer, is all but irrational – it may even trigger positive health behaviours.[50] Instead, becoming aware of how you relate to difficult thoughts, emotions or painful bodily sensations may be more helpful than focusing on the specific contents of thoughts, emotions and bodily sensations.

This is where mindfulness comes into play: the practice of mindfulness enables participants to make a radical shift in how they relate to their thoughts, feelings, and body sensations, as well as to outer circumstances. They recognize habitual, conditioned modes of reacting, and learn to disengage from them.[49] As such, MBIs focus on growing the capacity to embrace the unequivocal reality of living with cancer, and the ability of paying kind attention and of choosing freely and deliberately how you want to go about dealing with these thoughts, emotions, and bodily sensations, without having to get rid of them.

Evidence for the effectiveness of MBIs in oncology has rapidly increased in the last two decades. A meta-analysis of 29 RCTs with a total of 3439 patients[51] report reduction of psychological distress in cancer patients with a small to medium effect size (Hedges'*g* = .30). MBIs have beneficial effects on depression, anxiety, fear of cancer recurrence and fatigue.

Although first results indicate that MBIs are cost-effective in cancer care[52, 53], cost-effectiveness evaluations of MBIs are scarce.[54] A study in 129 breast cancer patients suffering from persistent pain explored cost-effectiveness of MBCT compared to wait-list control. At a Willingness to Pay (WTP) for a Quality adjusted life year (QALY) gained of €0, MBCT was cost-effective with a probability of 85% and remained cost-effective with a probability of 70% to 82% when smaller effects and higher MBCT costs were assumed.[52] Another study in 104 breast cancer patients compared the cost-effectiveness of Mindfulness-Based Stress Reduction (MBSR) to wait-list controls and concluded that MBSR was more expensive, but also slightly more effective than a waitlist control group.[53] Another study in 191 breast cancer patients investigated the cost-effectiveness of an adapted MBI with a different focus: Mindfulness-Based Art Therapy (MBAT). MBAT was compared to an active support group intervention employing a healthcare perspective. MBAT demonstrated the potential to achieve an equal trade-off between costs and effects with the support group intervention if some intervention-related costs were reduced.[55]

MBIs are also being delivered via Internet, but research on Internet-based MBIs (eMBIs) mostly focus on the efficacy of eMBIs in the general public. A recent review of 15 RCTs on eMBIs for the general public demonstrated a small but significant beneficial impact on depression, anxiety, well-being and mindfulness. The largest effect was found for stress, with a moderate effect size (Hedges' g=0.51).[56] For stress and mindfulness, exploratory subgroup analyses indicated that guided eMBIs had higher effect sizes than unguided eMBI, which are MBIs delivered through technological platforms without a therapist. Nevertheless, a review of 10 studies on unguided eMBIs provided initial support for unguided eMBIs in the general public as well.[57]

Studies focusing on the efficacy of eMBIs in cancer patients are scarce. One single controlled study (n=62) demonstrated feasibility of adapted Internet-based MBSR for cancer patients.[58] Another pilot study confirmed that MBSR delivered via an iPad may be feasible and acceptable for breast cancer patients.[59] In addition, an uncontrolled cohort of 257 fatigued patients showed significant improvements in fatigue and psychological distress after individual eMBCT.[60]

Although MBIs have previously demonstrated their potential as an alternative psychological treatment for cancer patients, a well-designed RCT comparing both individual Internet-based MBCT and group-based MBCT for cancer patients has never been conducted.

THESIS OUTLINE

This thesis focuses on an eMBI which already existed in clinical practice, which is an achievement on the account of the Helen Dowling Institute. The Helen Dowling Institute (HDI) is the oldest mental healthcare institute for cancer patients and their partners in The Netherlands. In order to improve patient-friendliness and accessibility of MBIs in cancer patients, the Helen Dowling Institute started to provide individual Internet-based MBCT (eMBCT) for cancer patients in clinical practice over ten years ago. In addition, the Radboud University Medical Centre for Mindfulness has gained experience in providing patient care and conducting research projects on MBIs in several patient groups, including cancer patients, since 2008. In 2012, the HDI and the Centre for Mindfulness combined forces and engaged in a collaborative research project comparing clinical and cost-effectiveness of both group-based MBCT and Internet-based MBCT (eMBCT) compared to Treatment as Usual (TAU). This thesis aims at researching these two interventions on clinical and cost-effectiveness outcomes compared to TAU.

Chapter 2 illustrates how psychiatric disorder and psychological distress are related to healthcare utilization in cancer patients. The research question in this chapter is: "*Are psychiatric disorder and psychological distress associated with increased healthcare utilization and increased healthcare costs?*" To answer this question, patients were assessed with Structured Clinical Interview for DSM-IV-TR Axis I Disorders (SCID-I) for depressive, anxiety, and/or adjustment disorder. The Hospital Anxiety and Depression Scale-questionnaire measured psychological distress. Retrospective self-reported healthcare utilization over the past 3 months was collected and associations between psychiatric disorder, psychological distress and healthcare utilization and costs per healthcare utilization category (mental, primary, somatic, and complementary) were assessed.

Chapter 3 describes the design and protocol of the BeMind study. The BeMind study examines the effectiveness of both group-based and Internet-based MBCT compared to TAU in reducing psychological distress by conducting a multicentre randomized controlled trial in a sample of 245 (mildly) distressed cancer patients. We reported detailed information on the methodological aspects of the trial, including its design,

eligibility criteria, study procedure, outcome measures, sample size calculation and statistical analyses. The research question of the BeMind study is: "*What is the effectiveness of both group-based and Internet-based MBCT compared to TAU in distressed cancer patients?*"

Chapter 4 describes the results of the BeMind study. In total, 245 cancer patients were randomly assigned to MBCT (*n*=77), eMBCT (*n*=90) or TAU (*n*=78). The effectiveness of both interventions compared to TAU was evaluated at post-treatment in terms of the primary outcome psychological distress and secondary outcomes fear of cancer recurrence, rumination, health-related quality of life, mindfulness skills and positive mental health.

Chapter 5 aims to determine how cancer patients and their mindfulness therapists experience participating in Internet-based MBCT. Therefore, the chapter describes the results of individual post-treatment interviews with 31 patients and a focus group interview with 8 therapists on experienced facilitators and barriers during Internet-based MBCT. The research question was "*What facilitators and barriers do patients and therapists experience in individual asynchronous therapist-assisted Internet-based MBCT?*"

Chapter 6 describes the results of the cost-effectiveness evaluation of both group-based and Internet-based MBCT compared to TAU. The research question is: "*Are both group-based and Internet-based MBCT cost-effective treatments from a societal perspective compared to TAU?*" Therefore, we conducted a cost-utility trial from the societal perspective along-side the three-armed clinical RCT.

Chapter 7 gives a summary of the main findings followed by a general discussion of the results in the light of the current literature, strengths and limitations of the research project, directions for future research and a reflection on the implementation of MBCT for cancer patients in regular healthcare.

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Chapter 2

Associations between psychiatric disorder, psychological distress and healthcare utilization in cancer patients.

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ABSTRACT

Objective

The mental burden of cancer might elicit additional healthcare utilization. However, it is unclear how psychiatric disorder and psychological distress relate to healthcare utilization. Therefore, this study explores associations between psychiatric disorder, psychological distress and healthcare utilization. It was hypothesized that presence of psychiatric disorder and psychological distress were associated with increased healthcare utilization and costs.

Methods

The current study consisted of secondary analyses of baseline data of a larger randomized controlled trial. 245 mixed-cancer patients with at least mild symptoms of psychological distress (Hospital Anxiety and Depression Scale (HADS-T) ≥11) were mainly recruited via online media, participating centres and patient associations. Patients were assessed with SCID-I for depressive, anxiety and/or adjustment disorder. Psychological distress was measured by the HADS. Retrospective self-reported healthcare utilization in the past three months was collected. Associations between predictors and healthcare utilization in terms of incidence rate ratios and costs per category (mental, primary, somatic, complementary) were assessed by negative binomial, logistic and gamma regression.

Results

Eighty-nine (36.3%) patients suffered from psychiatric disorder, which was associated with mental healthcare utilization (*IRR*=1.63) and costs (*OR*=3.11). We observed a nonsignificant trend of somatic healthcare utilization in patients with psychiatric disorder. Psychological distress was associated with mental healthcare utilization (*IRR*=1.09) and costs (*OR*=1.09). Psychological distress was also associated with complementary healthcare utilization (*IRR*=1.03).

Conclusion

Psychiatric disorder and psychological distress were associated with mental healthcare use and costs. Psychological distress was associated with complementary healthcare use. Adequate assessment and referral to mental healthcare might prevent unnecessary healthcare utilization.

BACKGROUND

In 2025 and beyond, each year 20 million people worldwide will be diagnosed with cancer.[1] Many cancer patients suffer from cancer-related mental burden, or even psychiatric disorder. A meta-analysis of psychiatric disorder in oncological and hematological settings yielded a prevalence of 30 to 40%.[2] Major depressive disorders (14.9%), anxiety (10.3%) and adjustment disorders (19.4%) were most prevalent.[2] In addition to the mental burden, psychiatric disorder may also negatively affect somatic outcomes. Depression in cancer patients is related to a higher mortality, possibly due to smoking or reduced anticancer treatment adherence.[3]

In addition to psychiatric disorder, cancer-related mental burden is commonly operationalised as degree of psychological distress, which is defined as a multi-dimensional emotional experience that may interfere with the ability to cope with cancer and its consequences.[4] Although psychiatric disorder and psychological distress overlap conceptually, psychological distress is self-reported and extends along a continuum.[5] Psychological distress is also related to poorer treatment adherence [5] and mortality.[6]

There is emerging evidence that the mental burden of cancer patients might be associated with increased healthcare utilization. Faller et al. [7] studied mental healthcare utilization in a sample of 4020 German cancer patients. Psychiatric disorder appeared to be an correlate of mental healthcare utilization (*OR*=1.68) independently of symptoms of depression (*OR*=1.04) and anxiety (*OR*=1.08).[7] In addition, administrative data of 5055 heterogeneous-cancer patients indicated that depression was associated with non-mental healthcare visits (*OR*=1.76), emergency department visits (*OR*=2.45), overnight hospitalization (*OR*=1.81) and hospital readmission rates (*OR*=2.03).[8] No studies have been conducted on associations between anxiety or adjustment disorders and healthcare utilization in cancer patients.

Studies on psychological distress and healthcare utilization show similar patterns. Psychological distress was associated with mental healthcare utilization in a study on 1602 Swiss childhood cancer survivors. Moreover, survivors not using mental healthcare more often used somatic healthcare.[9] In another large cross-sectional sample of 4326 heterogeneous-cancer survivors and 57109 non-cancer patients, psychological distress was associated with increased use of outpatient and inpatient hospital healthcare, emergency healthcare, and prescription medication.[10]

Moreover, use of complementary and alternative care in cancer patients has long been recognized.[11, 12] Previous studies have demonstrated associations between psychological distress symptoms and use of complementary healthcare services [13, 14], although evidence for this association is mixed.[15]

Thus, evidence suggests that both psychiatric disorder and psychological distress are associated with healthcare utilization in cancer patients. However, it is unclear how psychiatric disorder and psychological distress are associated with utilization of healthcare other than mental healthcare.

Therefore, the aim of this study was to provide a descriptive account of the associations between psychiatric disorder, psychological distress and mental, primary, somatic and complementary healthcare utilization. It was hypothesized that both psychiatric disorder and psychological distress would be associated with increased healthcare utilization and increased healthcare costs.

METHODS

Patients and procedure

This study was a secondary analysis of a multi-site randomized controlled trial (RCT) examining group- and Internet-based Mindfulness-Based Cognitive Therapy (MBCT) versus treatment as usual for distressed cancer patients.[16] The current study uses the baseline data prior to randomization. Eligibility criteria for the RCT were: a) (history of) diagnosis of cancer, all types; b) a score of ≥11 on the Hospital Anxiety and Depression Scale (HADS); c) command of the Dutch language; d) computer literacy; e) stable on psychotropic medication for three months. Exclusion criteria were: a) severe psychiatric morbidity; b) (previous) participation in a mindfulness-based intervention. Patients were recruited between April 2014 and December 2015 (see Table 1 for recruitment details). After positive screening, exclusion criteria were assessed via telephone and patients were invited for a baseline interview. The study was approved by the local ethics committee (CMO Arnhem-Nijmegen 2013/542).

Assessments

Demographic and clinical information

Demographic and clinical information included: gender, date of birth, marital status, children and level of education, type of cancer diagnosis, anticancer treatment intent

(curative/palliative), current active anticancer treatment. When patients were unsure about their anticancer treatment intent the researchers sought advice from a consultant oncologist.

Psychiatric disorder

Presence of psychiatric disorder was assessed by the SCID-I [17] which is a semi-structured psychiatric interview for DSM-IV-TR Axis I disorders. In this study, the sections on current and past depressive disorder, current anxiety disorder and current adjustment disorder were used. The SCID-I was administered by trained interviewers (FC and two research assistants). Two psychiatrists (EB and AS) and one psychologist (ML) supervised the administration of the SCID-I interviews and double-rated (*n*=97) of the audiotapes. Double-rated interviews were discussed together. The opinion of the supervisor was leading.

Psychological distress

Psychological distress was measured by the Hospital Anxiety and Depression Scale (HADS), a 14-item self-report scale that was originally developed to screen for anxiety and depression in medical outpatient clinics.[18] Internal consistency as measured by Cronbach's α was .87 in the current sample. HADS-T has 7-item depression (HADS-D, α=.84) and anxiety (HADS-A, α=.80) subscales. The threshold of ≥11 corresponds to the threshold for screening for mental disorder in cancer patients.[19] Although the subscales of the HADS do not provide a good separation between anxiety and depression [20], we chose to explore the original subscales keeping aforementioned limitations in mind.

Healthcare utilization

The Trimbos/iMTA questionnaire for Costs associated with Psychiatric illnesses (TiC-P) [21] generates retrospective self-reported quantitative data about healthcare utilization (type of healthcare, its duration and medication use). The recommended retrospective time horizon of 3 months was used. Healthcare utilization was operationalised as counts of visits across four categories: 1. Mental healthcare including visits to social workers, psychologists and psychiatrists; 2. Primary healthcare including visits to general practitioners, occupational physicians and physical- and occupational therapists; 3. Somatic healthcare including visits to medical outpatient clinics, emergency department, day healthcare units and overnight hospital stays. The costs analyses in the somatic healthcare category also included prescription medication costs; 4. Complementary healthcare utilization including visits to homeopaths, acupuncturists, traditional Chinese medicine and massage therapists. These categories were chosen on

basis of type of healthcare (mental vs. somatic), the distinction between primary and secondary healthcare, and insurance coverage (complementary healthcare is mostly out-of-pocket).

Healthcare costs

Cost estimates were derived from the Dutch reference manual for healthcare prices [22] and the Dutch website for national tariffs of prescription medications (https://www.medicijnkosten.nl). Cost estimates for dieticians and complementary healthcare providers were provided by their professional associations.

Data-analysis

Statistical analyses were run in IBM SPSS Statistics version 24. Patients with and without psychiatric disorder were tested for differences on clinical and demographical variables using *t*-test and chi-square tests. The data structurally demonstrated variances surpassing means (overdispersion). Negative binomial regression was used to evaluate the association of psychiatric disorder (depressive, anxiety and adjustment vs. no disorder) and psychological distress with healthcare utilization in terms of incidence rate ratios (*IRR*) per category. Negative binomial regression provides regression coefficients which denote differences in logs of expected counts per unit change in the predictor variable. Exponentiation of these regression coefficients gives the IRR (e.g. incidence rate ratio of healthcare utilization in the past three months per unit increase in the predictor). The difference of two logs is equal to the log of their quotient and therefore, we can interpret the parameter estimate as the log of the ratio of expected counts. This explains the "ratio" in incidence rate ratios. In addition, what is referred to as a count is technically a rate.

It is known that mental burden and healthcare utilization are associated with gender [23, 24], age [25, 26] cancer severity [27, 28] and being under cancer treatment.[28] Therefore, these possible confounders were included as covariates. In addition, this model specification also provided the best goodness-of-fit statistics (lowest AIC/BIC):

$$g(\,) = log(\,) = + {}_1 Ps.Distress / Ps.Disorder_1 + {}_2 Gender_2 + {}_3 Age_3 + {}_4 AnticancerTreatmentIntent_4 + {}_5 CurrentActiveCancerTreatment_5 \Rightarrow = e^{+1x1+2x2+3x3+4x4+5x5} = e^x\,(x1 = [1\, x_1\, x_2\, x_3\, x_4\, x_5])$$

The healthcare utilization cost data were non-negative and displayed positive skew. Therefore, the healthcare utilization outcome data in costs in Euros were analyzed by means of a two-part modeling strategy [29] using a) logistic regression to assess whether psychiatric disorder/psychological distress were associated with whether or not patients had costs per category and b) if patients had costs, gamma regression

with a log link function to assess whether psychiatric disorder/psychological distress were associated with amount of costs. There were no missing data. We did not exclude outliers.

RESULTS

In total, 532 patients were screened after which 98 (18.4%) were excluded. After telephone assessment of 434 patients, another 141 (32.5%) were excluded or refused participation. Of the remaining 293 patients, 48 (16.4%) refused participation. In total, 245 patients were randomized (see Table 1) and their baseline data were included in the current study.

There was considerable variability in tumour types, although the majority had breast cancer (*n*= 151, 61.6%). About one-third (36.3%) suffered from psychiatric disorder. Five (2.0%) patients suffered from a concurrent depressive and anxiety disorder. Of the five patients with concurrent anxiety disorders, only one patient had a main, cancer-related diagnosis. The other four anxiety disorders were social phobia (*n*=2) and specific phobia (*n*=2). These patients were therefore included in the depressive disorder-category only. Average HADS-T was 17.6 (*SD*=6.6). Patients with and without psychiatric disorder did not differ significantly on clinical and demographical variables (all *p*-values >.05). Table 2 provides descriptive statistics on overall healthcare utilization per category.

Patients with psychiatric disorder were significantly more likely to use mental healthcare (see Table 3) and had more mental healthcare costs (see Table 4), even although almost half (*n*=38, 42.7%) did not use mental healthcare. Moreover, patients with psychiatric disorder demonstrated a nonsignificant trend towards enhanced use of somatic healthcare. No such trend was found for somatic healthcare costs. Patients with psychiatric disorder were not more likely to use primary and complementary healthcare. Considering specific disorders, we only found a significant associations between depression and adjustment disorder and mental healthcare use but no association with costs.

TABLE 1: Baseline Sociodemographic and Clinical Characteristics (*n*=245)

Characteristic	*n*	%
Gender		
Female	210	85.7
Male	35	14.3
Age in years		
Mean	51.7	
SD	10.7	
Married / in a relationship		
Yes	202	82.4
No	43	17.6
Children		
No	76	31.0
Yes	169	69.0
Education		
High	166	67.8
Middle	77	31.4
Low	2	0.8
Diagnosis		
Breast cancer	151	61.6
Gynecological cancer	18	7.3
Prostate cancer	16	6.5
Colon cancer	12	4.9
Non-hodgkin lymphoma	11	4.5
Skin cancer	5	2.0
Thyroid cancer	4	1.6
Bladder cancer	4	1.6
Neuroendocrine tumour	4	1.6
Other	20	8.2
Time since diagnosis in years		
Mean	3.5	
SD	4.7	
Anticancer treatment intent		
Curative	206	84.1
Palliative	39	15.9
Current anticancer treatment		
None	133	54.2

TABLE 1: Continued

Characteristic	*n*	%
Hormone therapy	79	32.2
Combination of treatments	12	4.9
Immunotherapy	9	3.7
Radiotherapy	8	3.3
Chemotherapy	4	1.6
Psychiatric disorder		
All	89	36.3
Depressive	42	17.1
Anxiety	27	11.0
Adjustment	20	8.2
Psychological distress (HADS)*		
Total	17.7	6.6
Depression	8.2	3.8
Anxiety	9.4	3.7
Recruited via		
Online media (social media, website)	66	26.9
Patient associations	43	17.6
Participating mental healthcare centers	41	16.7
Offline media (advertorials, leaflets)	27	11.0
Attended by next-of-kin	27	11.0
Healthcare providers	23	9.4
Unknown/ could not remember	18	7.3

* Hospital Anxiety and Depression Scale

Patients with higher psychological distress were more likely to report having utilized mental healthcare (see Table 3) and had higher mental healthcare costs (see Table 4). Moreover, higher psychological distress was associated with more complementary healthcare visits, but not with more costs. Higher psychological distress was not associated with more visits to primary or somatic healthcare, although patients with higher psychological distress did have higher primary healthcare related costs. In the analyses separating the depression and anxiety subscales, patients with more depressive symptoms were more likely to visit mental and primary healthcare. Patients with more anxiety symptoms were more likely to visit mental and complementary healthcare. Higher scores on either subscale were not associated with somatic or complementary healthcare costs.

TABLE 2. Descriptives on healthcare utilization in the past 3 months: counts and costs (in Euros) per category (*n*=245)

Measure	Mental	Primary	Somatic	Complementary
Counts				
1 > visits: n	106	216	214	71
1 > visits: %	43.3	88.2	87.3	29
Mean	2	7.22	6.51	1.07
SD	3.56	7.98	8.3	2.35
Range	0-30	0-48	0-46	0-20
Costs				
Mean	121.27	280.51	1370.4	66.58
SD	221.01	403.27	2140.27	147.06
Range	0-1466	0-4604	0-14016	0-1250

TABLE 3. Incidence rate ratios (IRR) of healthcare utilization per independent variable and healthcare utilization category (*n*=245)

	Mental Healthcare Utilization IRR (95% CI)	Primary Healthcare Utilization IRR (95% CI)	Somatic Healthcare Utilization IRR (95% CI)	Complementary Healthcare Utilization IRR (95% CI)
Psychiatric disorder (yes/no)				
All	1.63 (1.18-2.25)**	0.93 (0.70-1.23)^{ns}	1.30 (0.98-1.72)^{ns}	1.18 (0.81-1.71)^{ns}
Depressive	1.71 (1.11-2.62)*	1.01 (0.70-1.46)^{ns}	1.34 (0.92-1.95)^{ns}	1.25 (0.78-2.01)^{ns}
Anxiety	1.43 (0.86-2.37)^{ns}	0.80 (0.51-1.26)^{ns}	1.35 (0.87-2.11)^{ns}	1.15 (0.63-2.10)^{ns}
Adjustment	1.77 (1.00-3.10)*	0.97 (0.59-1.61)^{ns}	1.15 (0.70-1.91)^{ns}	1.48 (0.77-2.83)^{ns}
Psychological distress (per point increase)				
Total	1.09 (1.06-1.12)**	1.02 (1.00-1.04)$^{ns\ ns}$	1.00 (0.98-1.03)^{ns}	1.03 (1.00-1.06)*
Depression	1.14 (1.09-1.19)**	1.04 (1.00-1.08)*	1.03 (0.99-1.07)^{ns}	1.04 (0.99-1.10)^{ns}
Anxiety	1.12 (1.07-1.18)**	1.02 (0.98-1.06)^{ns}	0.98 (0.94-1.02)^{ns}	1.06 (1.01-1.11)*

* $p < .05$, ** $p < .01$, $^{ns}p > .05$

TABLE 4: Odds ratios (OR) of presence of healthcare utilization costs in logistic regression and exponentiated coefficients in gamma regression on amount of costs (*n*=245)

	Mental healthcare costs		**Primary healthcare costs**		**Somatic healthcare costs**		**Complementary healthcare costs**	
	Logistic OR (95%CI)	Gamma β (95%CI)	Logistic OR (95%CI)	Gamma β (95%CI)	Logistic OR (95%CI)	Gamma β (95%CI)	Logistic OR (95%CI)	Gamma β (95%CI)
Psychiatric Disorder (yes/no)								
All	3.11^{**} (1.76-5.51)	$.97^{ns}$ (.71-1.33)	1.23^{ns} (.52-2.86)	1.08^{ns} (.84-1.40)	41825156.42^{ns} (.00-.00)	$.73^{ns}$ (.51-1.04)	1.12^{ns} (.63-1.99)	0.84^{ns} (.59-1.20)
Depressive	3.44^{**} (1.56-7.12)	1.16^{ns} (.77-1.73)	$.98^{ns}$ (.34-2.88)	1.01^{ns} (.72-1.40)	33739594.14^{ns} (.00-.00)	$.77^{ns}$ (.49-1.22)	1.46^{ns} (.69-3.11)	0.89^{ns} (.59-1.34)
Anxiety	3.92^{**} (1.58-9.73)	1.02^{ns} (.67-1.55)	1.83^{ns} (.39-8.65)	1.34^{ns} (.90-1.99)	53897986.09^{ns} (.00-.00)	$.68^{ns}$ (.38-1.19)	0.78^{ns} (.29-2.11)	$.77^{ns}$ (.44-1.35)
Adjustment	2.05^{ns} (.75-5.56)	$.75^{ns}$ (.44-1.26)	1.25^{ns} (.26-6.00)	$.94^{ns}$ (.58-1.51)	42073575.54^{ns} (.00-.00)	$.91^{ns}$ (.49-1.67)	1.28^{ns} (.47-3.48)	$.73^{ns}$ (.41-1.27)
Psychological Distress (per point increase)								
Total	1.09^{**} (1.04-1.14)	1.04^{**} (1.01-1.07)	1.03^{ns} (.97-1.10)	1.02^{ns} (1.00-1.04)	1.15^{ns} (.99-1.35)	1.01^{ns} (.98-1.03)	1.04^{ns} (.98-1.07)	1.01^{ns} (.99-1.04)
Depression	1.16^{**} (1.07-1.25)	1.02^{ns} (.98-1.06)	1.08^{ns} (.97-1.20)	1.04^{*} (1.00-1.07)	1.32^{ns} (.97-1.80)	1.03^{ns} (.98-1.08)	1.04^{ns} (.97-1.13)	1.01^{ns} (.96-1.06)
Anxiety	1.11^{**} (1.03-1.20)	1.11^{**} (1.05-1.16)	1.02^{ns} (.91-1.14)	1.02^{ns} (.98-1.06)	1.21^{ns} (.93-1.57)	0.98^{ns} (.93-.1.03)	1.04^{ns} (.96-1.12)	1.03^{ns} (.99-1.08)

$^{*}p < .05$, $^{**}p < .01$, $^{ns}p > .05$

DISCUSSION

This study explored how psychiatric disorder and psychological distress are associated with healthcare utilization and costs. Patients with psychiatric disorder, most notably depressive and adjustment disorder, were more likely to visit mental healthcare and have higher mental healthcare costs. Patients with psychiatric disorder also demonstrated a nonsignificant trend towards enhanced use of somatic healthcare. Furthermore, patients with higher psychological distress were more likely to report having utilized mental and complementary healthcare and were more likely to demonstrate mental healthcare-related costs.

Although the percentage of patients with psychiatric disorder having received mental healthcare was higher than reported previously (57.3 vs. 43.6 [8]), about half of patients with psychiatric disorder did not use mental healthcare. This is in line with research demonstrating that there is no one-on-one relationship between positive screen for psychological distress and subsequent wish for or use of mental healthcare.[30] For example, distressed patients could also choose to rely on family or prefer to not talk about it.[30] Moreover, lack of organizational and therapeutic integration of psycho-oncological services in routine oncology care is a known barrier to using psychological services.[31] Ideally, mental healthcare professionals inform and support patients in making a conscious decision on their psychological needs and wishes.[32]

Patients with psychiatric disorder demonstrated a nonsignificant trend towards more use of somatic healthcare. A previous study found associations between depression and somatic healthcare utilization.[8] Patients with depression are perhaps more likely to somatize, amplify their symptoms and be more aware of bodily sensations, rendering them more likely to seek help in non-mental healthcare.[33] Psychiatric disorder was not associated with more costs. The present use of reference data on healthcare costs might have resulted in a too crude approximation of actual healthcare costs. Bottom-up micro-costing endeavours, aiming to determine every cost item involved of a specific healthcare procedure, could have translated into cost data more sensitive to presence of psychiatric disorder.

Both patients with depression and adjustment disorder showed increased mental healthcare utilization. Patients with anxiety disorder did not. Feelings of anxiety might be normalized in context of cancer, so anxiety disorder is often overlooked by healthcare providers.[34] Furthermore, although patients with adjustment disorder demonstrated more mental healthcare related visits, only anxiety disorder was associated with increased mental healthcare-related costs. Most likely, this inconsistent finding is caused

by analytical differences between the count and cost data. Furthermore, separate diagnoses of depression, anxiety and adjustment disorder were unrelated with visits or costs in primary, somatic or complementary healthcare. However, the separate analyses of specific disorders had a reduced sample size which may have led to underpowered analyses.[35]

Psychological distress appeared to be associated with visits to mental and complementary healthcare. The finding that complementary healthcare use was related to psychological distress, mainly anxiety symptoms, reflects earlier findings. [13, 14] In our sample, 29% of the cancer patients appeared to use complementary healthcare even though this is often not fully reimbursed by healthcare insurance in The Netherlands. Although psychological distress was associated with complementary healthcare utilization, the majority (56%) using complementary healthcare did so without simultaneously consulting a mental healthcare professional. Patients resorting to complementary care might fear the stigma of mental healthcare, or they might prefer complementary approaches to improve their mental well-being. Some have argued that complementary healthcare use in distressed cancer patients is a sign of a lack of integration of psycho-oncological services.[36] This reiterates the point that mental healthcare professionals should be available to facilitate cancer patients to make a conscious choice whether, and how, they want to alleviate their mental burden.

The absence of an association between psychological distress and somatic healthcare utilization contradicts previous findings of Han et al. [10] that cancer survivors with severe psychological distress use more somatic healthcare services. A possible explanation for this difference might be that in The Netherlands, the general practitioner is the gatekeeper to somatic healthcare, and might prevent somatic healthcare by referring cancer patients to mental health services instead. Supporting this explanation, tentative results indicate an association between depressive symptoms and primary healthcare visits.

Future studies should substantiate the association between psychiatric disorders and somatic healthcare utilization to determine whether appropriate referral to mental healthcare in cancer patients possibly contributes to decreased utilization of somatic healthcare. Furthermore, more research is needed on the nature, outcomes and costs of complementary healthcare use. For some patients, referral to professionals offering evidence-based mental healthcare might be a better option than letting them seek their refuge with complementary healthcare providers offering less appropriate interventions.

Study limitations

Our study sample was selective: self-referred, at least mildly distressed and interested in a Mindfulness-Based intervention. Moreover, the large majority of our patients were highly educated, female, Caucasian, had breast cancer and were treated with curative intent, so our sample was relatively homogenous. Although we cannot extrapolate our findings to all Dutch distressed cancer patients, these characteristics are in concordance with characteristics of cancer patients receiving psychosocial healthcare in The Netherlands.[37] Due to the cross-sectional nature of the data, we cannot rule out alternative explanations such as the possibility that increased healthcare utilization could increase mental burden.

Ideally, we would have used medical chart data of both primary healthcare and/or hospitals to check the reliability of the clinical and self-reported healthcare utilization data. We did not have access to data on cancer stages and co-morbid medical conditions. Moreover, self-reported healthcare utilization data are most likely less reliable. Therefore, all healthcare utilization data were gathered using an interview-based format and filled out together with a researcher to ensure reporting accuracy and completeness. Nevertheless, it remains possible that self-reported healthcare utilization was affected by psychiatric disorder, as it is known that depressive disorder affects memory functions. [38]

Lastly, limitations inherent to the explorative nature and research questions of the current study should be mentioned: performing multiple testing without adjustment may have resulted in chance findings and psychiatric disorder and psychological distress were not compared head-to-head against each other.

Clinical implications

Notwithstanding the limitations, the results of our study suggest that there is room for improvement in terms of mental healthcare for cancer patients. A large proportion of cancer patients remains under the radar of mental healthcare. Patients scoring above the cut-off for psychiatric disorder should be offered further psychiatric diagnostics. Ideally, multiple methods are available to identify psychological needs of cancer patients [32], and mental healthcare professionals gauge patients' needs and wishes. They can support patients in making a conscious choice to rely on family, refrain from seeking (regular) help, or to participate in evidence-based treatment such as cognitive behavioral therapy [39] or mindfulness-based interventions.[40]

Conclusion

This study explored how psychiatric disorder and psychological distress are associated with healthcare utilization and costs. Patients with psychiatric disorder were more likely to visit mental healthcare and have more mental healthcare costs. Furthermore, patients with higher psychological distress were more likely to report having utilized mental and complementary healthcare and were more likely to demonstrate mental healthcare-related costs. Appropriate referral of cancer patients who are both in need of and receptive to psychological treatment could not only result in improved well-being of cancer patients, but also in a reduction of non-mental healthcare utilization.

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Chapter 3

Study protocol of a multicenter randomized controlled trial comparing the effectiveness of group and individual Internet-based Mindfulness-Based Cognitive Therapy with treatment as usual in reducing psychological distress in cancer patients: the BeMind study

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ABSTRACT

Background

Mindfulness-based interventions have shown to reduce psychological distress in cancer patients. The accessibility of mindfulness-based interventions for cancer patients could be further improved by providing mindfulness using an individual Internet-based format. The aim of this study is to test the effectiveness of a Mindfulness-Based Cognitive Therapy (MBCT) group intervention for cancer patients in comparison with individual Internet-based MBCT and treatment as usual (TAU).

Methods/Design

A three-armed multicenter randomized controlled trial comparing group-based MBCT to individual Internet-based MBCT and TAU in cancer patients who suffer from at least mild psychological distress (Hospital Anxiety and Depression Scale (HADS) ≥ 11). Measurements will be conducted prior to randomization (baseline), post-treatment and at 3 months and 9 months post-treatment. Participants initially allocated to TAU are subsequently randomized to either group- or individual Internet-based MBCT and will receive a second baseline measurement after 3 months. Thus, the three-armed comparison will have a time span of approximately 3 months. The two-armed intervention comparison includes a 9-month follow-up and will also consist of participants randomized to the intervention after TAU. Primary outcome will be post-treatment psychological distress (HADS). Secondary outcomes are fear of cancer recurrence (Fear of Cancer Recurrence Inventory), rumination (Rumination and Reflection Questionnaire), positive mental health (Mental Health Continuum – Short Form), and cost-effectiveness (health-related quality of life (EuroQol –5D and Short Form-12) and healthcare usage (Trimbos and iMTA questionnaire on Costs associated with Psychiatric illness). Potential predictors: DSM-IV-TR mood/anxiety disorders (SCID-I) and neuroticism (NEO-Five Factor Inventory) will be measured. Mediators of treatment effect: mindfulness skills, (Five-Facets of Mindfulness Questionnaire- Short Form), working alliance (Working Alliance Inventory) and group cohesion (Group Cohesion Questionnaire) will also be measured.

Discussion

This trial will provide valuable information on the clinical and cost-effectiveness of group versus Internet-based MBCT versus TAU for distressed cancer patients.

BACKGROUND

Cancer is a major healthcare challenge. Cancer causes more than a quarter of all deaths in OECD countries with more than 5 million new cases diagnosed every year, averageing about 261 cases per 100 000 people.[1] In The Netherlands it is expected that the incidence of cancer will increase with more than 40% between 2007 and 2020.[2] These numbers indicate that we are looking at a steadily increasing number of patients who will have to cope with cancer in the near future.

Living with cancer is a psychological burden. In a review of the prevalence of depression, anxiety and adjustment disorders in cancer patients in both palliative and non-palliative settings it was found that about one third of all patients suffer from a mood disorder in the first five years after diagnosis.[3] A recent epidemiological survey based on more than 2000 structured clinical interviews across major tumour entities found the most prevalent mental disorders to be anxiety (11.5%) adjustment (11.1%) and depressive disorders (6.5%).[4] Considering the rising prevalence of people living with cancer, the absolute number of cancer patients in need of psychological treatment is expected to increase. Addressing this increasing need calls for effective, widely available and accessible psychological treatment.

In recent years, many studies have assessed the effect of mindfulness-based interventions for cancer patients. Mindfulness is defined as intentionally paying attention to moment-by-moment experiences in a non-judgmental way.[5] Mindfulness-Based Stress Reduction (MBSR) [6] and Mindfulness-Based Cognitive Therapy (MBCT) [7], the latter developed specifically to prevent relapse in depression, are protocols designed to teach the cultivation of mindfulness. In a review of 22 studies, mindfulness-based interventions were found to be moderately effective in reduction of symptoms of anxiety and depression in cancer patients.[8] Recently, another randomized controlled trial (RCT) showed that mindfulness-based treatment was superior to both supportive-expressive group therapy and a 1-day stress management condition in improving a range of psychological outcomes in a sample of 271 distressed breast cancer survivors.[9] Although any follow-up results should still be considered preliminary, the recent review indicates that effect sizes (ES) at follow-up were significant with small to moderate ESs for nonrandomized studies and small ESs for RCTs.

Psychological treatment for cancer patients implies treatment for people who have difficulty with travelling due to cancer -related impairments or fatigue. Also, treatment scheduling should be flexible, allowing for adaptation to individual circumstances, for example ongoing radio- or chemotherapy. Taking this into account, Internet-

based treatment might hold promise to address these problems. A recent review concludes that guided Internet-based Cognitive Behavioural Therapy (CBT) "appears to be a promising and effective treatment for chronic somatic conditions to improve psychological and physical functioning and disease-related impact".[10] In addition to its clinical effectiveness, research also suggests evidence for the cost-effectiveness of Internet-based CBT for somatic populations.[11, 12]

Literature on the effectiveness of Internet-based mindfulness treatment is still scarce. There are a few studies in non-clinical populations which show that Internet-based mindfulness treatment resulted in an improvement of mindfulness skills and reduction of perceived distress.[13-15] Recently, encourageing evidence was presented for the feasibility and efficacy of Internet-based mindfulness treatment in a study of 62 underserved and distressed cancer patients.[16] Compared to treatment as usual (TAU) patients reported an increase of mindfulness and a reduction of depressive and stress symptoms. This provides preliminary evidence for the effectiveness of Internet-based mindfulness treatment compared to TAU.

Direct comparisons of Internet-based mindfulness treatment to existing group treatments for distressed cancer patients are absent, let alone follow-up comparisons. One of the biggest challenges in internet intervention research is low treatment adherence [17] which affects treatment effectiveness.[18] A recent study of Internet-based MBCT for treatment of chronic cancer-related fatigue using a treatment format similar to ours indicated a non-adherence rate of 38%, which is higher than in comparable face-to-face interventions.[19] The current trial will provide the first description of the relative long-term effectiveness of group- compared to Internet-based MBCT by including a follow-up measurement up to 9 months post-treatment and keeping close track of treatment adherence in both intervention arms.

Thus, it is unknown whether Internet-based MBCT has similar effectiveness as group-based MBCT in alleviating distress in cancer. Therefore, we primarily compare post-treatment psychological distress between group-based and Internet-based MBCT. Also, effectiveness in reducing psychological distress up to nine months post-treatment will be compared between group- and Internet-based MBCT. Moreover, we would like to determine whether the two interventions could reduce fear of cancer recurrence and rumination. Also, at the other end of the psychological spectrum, both group- and Internet-based MBCT might be able to improve positive mental health in cancer patients compared to TAU. Furthermore, alongside the clinical trial, cost-effectiveness of both MBCT interventions compared to TAU will be determined. We expect both interventions to be cost-effective compared to TAU.

We do not expect all individuals to benefit similarly from the two interventions. Therefore, studying predictors of each intervention's effect potentially enables us to determine who benefits most from what treatment – group-based or Internet-based MBCT. In this study we would like to explore two possible predictors: the presence/absence of a DSM-IV-TR mood/anxiety disorder and the personality trait neuroticism.

Research on mindfulness-based interventions for cancer patients has focused on the prevalence and treatment of distress rather than psychiatric disorders. Not much is known on the effectiveness of MBCT in oncology patients suffering from a mood and/or anxiety disorder as opposed to patients suffering from distress. We are interested to see if the presence of a psychiatric disorder is a better predictor of treatment outcome than psychological distress.

Moreover, previous research has shown that a high score on neuroticism has a negative effect on (group) psychotherapy outcome.[20] This study aims to explore the hypothesis that higher neuroticism at baseline has a negative predictive value for the primary outcome measure and to explore possible differences in treatment outcome between group- and Internet-based MBCT.

As it is known that mindfulness skills mediate the relationship between mindfulness practice and improvements in psychological symptoms (e.g. [21]), we hypothesize that the improvement on the Hospital Anxiety and Depression Scale (HADS) in the MBCT intervention arms is mediated by mindfulness skills. Moreover, weekly measurements (MAAS and I-PANAS-SF) will be used to test the hypothesis that an increase in mindfulness skills antedates changes in affect during the intervention.

One of the differences between face-to-face and online treatment is the relationship with the therapist. Working alliance, or therapeutic alliance, is a long-recognized concept in psychotherapy research. Although it is known that a working alliance is realizable in Internet-based therapy [22], little is known about the possible difference in working alliance between group- and Internet-based MBCT. We would be interested to see if working alliance mediates the relationship between intervention and outcome in both interventions.

The relationship with both the therapist and other group members in group-based treatment, or group cohesion, is often considered to be one of the most important contributors to positive treatment effect in group therapy. The current study aims to assess whether group cohesion mediates the relationship between the group-based MBCT intervention and outcome.

In conclusion, the primary aim of this study is to compare the effectiveness of group- and Internet-based MBCT to TAU to reduce distress in cancer patients after treatment. Secondary outcome measures will be fear of cancer recurrence, rumination, and positive mental health. In addition, possible effect predictors (DSM-IV-TR mood/anxiety disorder and neuroticism) and mediators (mindfulness skills, working alliance, group cohesion) of treatment outcome will be explored. In order to determine the long-term stability of intervention effects, assessments will take place 3 and 9 months post-treatment. Alongside the clinical trial, the cost-effectiveness of both MBCT interventions compared to TAU will be determined. As far as we know, this is the first direct comparison between group-based MBCT, Internet-based MBCT and TAU.

METHODS/DESIGN

Study design

This study is a multicenter, parallel group randomized controlled trial. Participants are randomized to group-based MBCT, Internet-based MBCT or TAU. Participants initially randomized to TAU are subsequently randomized to either group- or Internet-based MBCT which participants receive after a waiting-list period of three months. During the waiting-list period, participants know which treatment they will receive after the waiting list and participants are allowed to receive care as usual, except for any mindfulness-based intervention. The study protocol has been approved by our ethical review board (CMO Arnhem-Nijmegen) and is registered under number 2013/542.

Setting

The group MBCT is provided at the Radboud University Medical Centre in Nijmegen, the Jeroen Bosch Hospital in 's Hertogenbosch and at four mental health institutes specialized in psycho-oncology (Helen Dowling Institute (Bilthoven), Ingeborg Douwes Centrum (Amsterdam), De Vruchtenburg (Leiden), Het Behouden Huys (Haren)). The Internet-based MBCT has been developed with, protected and hosted by IPPZ, a commercial e-health company in The Netherlands. Patients receive an invitational e-mail with the conditions of use. The Internet-based MBCT is accessed using a personal double-step-verification- protected webpage on the participants' own personal computer, mobile phone or tablet device.

Study population

Inclusion criteria of the study are a) a cancer diagnosis, any tumour or stage b) a score of 11 or higher on the Hospital Anxiety and Depression Scale (HADS), c) computer literacy

and internet access d) a good command of the Dutch language and e) willingness to participate in either MBCT intervention. Exclusion criteria are a) severe psychiatric morbidity such as suicidal ideation and/or psychosis b) change in psychotropic medication dosage within a period of three months prior to baseline c) current or previous participation in a mindfulness-based intervention (> 4 sessions of MBCT or MBSR).

Procedure

Participants are recruited in aforementioned participating centers and recruited via social media, patient associations and advertorials in local newspapers. Patients who are interested in participation can enroll themselves at our website (**www.bemind.info**) at which point they complete the HADS. Patients with a score of 11 or higher are contacted by telephone by one of the researchers. During this call more information about the study is provided and eligible patients are invited for a research interview. The subsequent research interview is conducted face-to-face or by telephone depending on participant preference. Written informed consent, demographic and clinical characteristics are obtained on paper via regular mail. Subsequently the Structured Clinical Interview for DSM-IV-TR Axis-I disorders (SCID-I) is administered to diagnose possible mood/anxiety disorders and the Trimbos and iMTA questionnaire on Costs associated with Psychiatric illness (TiC-P) to assess medical and productivity loss costs. The participant completes the remainder of the (self-report) questionnaires online.

Randomization

Randomization is stratified for setting and minimized for a) gender, b) stage of disease (curative *versus* palliative) and c) type of cancer (breast cancer *versus* other). Randomization is computerized using a randomization website specifically designed for the current study. Randomization is conducted by one of the researchers (EB) who is not involved in the follow-up assessments.

Follow-up assessments

Follow-up assessments take place directly post-treatment and at three and nine months follow-up. The follow-up assessments are similar to the baseline assessment: participants are contacted by telephone in order to re-administer the SCID-I and the TiC-P and participants receive an online survey with the self-report scales. In case of dropout, the researcher tries to contact the participant at least three times to complete the outcome measures and to identify the main reason for dropout.

Intervention

The MBCT curriculum used in both group and Internet-based MBCT interventions is primarily based on the MBCT program by Segal, Williams and Teasdale.[23] The program was adapted to the oncology patient in terms of tailoring psycho-educative elements to themes relevant to the cancer patient (e.g. cancer-related fatigue) and adapted movement exercises (for patients suffering from edema). In both conditions, participants receive guided mindfulness meditation exercises for home practice and a reader with home practice instructions and background information.

The group-based MBCT curriculum consists of 8 weekly 2,5 hour group sessions, a silent day between session six and seven and home practice assignments of about 45 minutes, 6 days per week (see table 2). During the weekly sessions the teacher guides different mindfulness exercises and introduces new exercises, and home practice assignments are discussed.

The Internet-based MBCT intervention is similar to group MBCT in curriculum content, but different in delivery. Participants in the Internet-based MBCT intervention log in on a secure personal webpage where all content relevant to that week's session can be downloaded. Participants are asked to read the weekly information and do the mindfulness exercises and write down their experiences in their personal log. They are encouraged to correspond with their personal teacher about their practice experiences via a secure, integrated mailing system. The teacher replies to this log on a predetermined day of the week and guides the participant through the curriculum. Participants can continue with next weeks' session only after registering their experiences in their log for the previous week. Participants are encouraged to follow the intervention within the nine-week structure. However, the teacher can decide to extend this period in case of illness or holidays.

All teachers fulfill the advanced criteria of the Association of Mindfulness-based Teachers in The Netherlands and Flanders) which are in concordance with the UK Mindfulness-Based Teacher Trainer Network Good Practice Guidelines for teaching mindfulness-based courses [24], including a minimum of 150 hours of education in MBSR/MBCT background and theory, training in teaching formal and informal meditation practices, psycho-education and inquiry, supervision and giving an MBSR or MBCT course including a reflection report, b) relevant professional training, c) minimum of three years of practicing meditation regularly and attending retreats, d) having attended MBSR/MBCT as a participant, e) continued training and f) giving a minimum of two courses per two year. Three full-day plenary supervision meetings are held during the intervention phase of the trial, consisting of mindfulness practices, workshops, small group teachings

and plenary discussions about difficulties or practical issues. All teachers are involved in both group and Internet-based MBCT. Teachers without prior Internet-based MBCT experience are provided with guidelines and supervised by more experienced Internet-based MBCT teachers.

In the group-based MBCT condition, sessions are videotaped to evaluate teacher competence and protocol adherence using the Mindfulness-Based Interventions - Teachers Assessment Criteria (MBI-TAC).[25] The MBI-TAC was translated to Dutch using the guidelines of the International Test Commission.[26] Group-based MBCT participants are requested to complete the same form for their teachers' competence. As the MBI-TAC is not applicable to Internet-based treatment and there are currently no other ways to evaluate teacher competence in Internet-based mindfulness treatment, teacher competence will not be assessed in the Internet-based condition using a standardized measurement.

Primary outcome measure

Psychological distress

For a measurement scheme we refer to Table 1. The primary outcome measure is the post-treatment total score on the HADS, a 14-item self-report screening scale that was originally developed to indicate the possible presence of anxiety and depressive states in the setting of a medical outpatient clinic.[27, 28] As earlier research in a palliative setting suggested the total HADS score should be used, this score will be used rather than individual depression and anxiety subscales.[29] The HADS shows good psychometric properties in the general medical population, including oncology patients in palliative phase.[30] Internal consistency as measured with Cronbach's α varied from .84 to .90. [28, 31] Test-retest reliability was good as Pearson's $r > .80$ were obtained.[28, 32]

Secondary outcome measures

Fear of cancer recurrence

Fear of cancer recurrence is assessed with the Fear of Cancer Recurrence Inventory (FCRI; [33]). This 42-item 4-point Likert scale questionnaire has been found to have a robust factor structure with Cronbach's $\alpha=0.75$ to 0.91 across subscales and test-retest reliabilities over a two-week interval of 0.58 to 0.83 across subscales. The FCRI is positively associated with other measures of anxiety symptoms, intrusive thoughts and avoidance and negatively associated with quality of life in a large sample of cancer patients.[33]

TABLE 1: Measurement scheme

Variable goal	Measure	Target	Screening	T0	During	T0b TAU only	T1	T2	T3
Primary outcome	HADS	Psychological distress	x	x		x	x	x	x
Secondary outcomes	FCRI	Fear of cancer recurrence		x		x	x	x	x
	RRQ	Rumination Reflection Questionnaire		x		x	x	x	x
	MHC-SF	Mental Health Continuum – Short Form		x		x	x	x	x
Effect predictors	SCID	DSM-IV Axis I disorders		x		x	x	x	x
	NEO-FFI	Personality dimensions		x					x
Process measures	FFMQ-SF	Mindfulness skills		x		x	x	x	x
	WAI	Working alliance			x				
	GCQ	Group cohesion			x				
	MAAS	Mindfulness skills			x				
	I-PANAS-SF	Mood			x				
	Calendar	Mindfulness adherence			x				
Cost-effectiveness	TiC-P	Healthcare costs and productivity		x		x	x	x	x
	EQ-5D	Health-related quality of life		x		x	x	x	x
	SF-12	Health-related quality of life (general health)		x		x	x	x	x

Rumination

Rumination is measured by the rumination subscale of the Rumination and Reflection Questionnaire (RRQ; [34]). Subjects rate their level of agreement of disagreement on a five-point rating scale (e.g., "I always seem to be re-hashing in my mind recent things I've said or done"). The Dutch version has Cronbach's alphas ranging between .88 and .93.[35]

Positive mental health

Positive mental health is measured by the Mental Health Continuum-Short Form (MHC-SF; [36]) which comprises 14 items, representing various feelings of well-being in the past month rated on a 6-point Likert scale (never, once or twice a month, about once a week, two or three times a week, almost every day, every day). The MHC-SF contains

three subscales: emotional, psychological and social well being. The short form of the MHC has shown excellent internal consistency (> .80). The test-retest reliability of the MHC-SF over three successive 3 month periods was .68 and the 9 month test-retest in a Dutch sample was .65.[37]

Medical and societal costs

Data on medical and societal costs and data on health-related quality of life are collected to conduct the cost-effectiveness – analysis. Data on medical and societal costs are gathered using the TiC-P.[38] The TiC-P generates quantitative data about direct healthcare utilization (the type of care, its duration and medication) and indirect societal costs (cancer-related absence from work and cancer-related impairment in non-paid work). Unit cost estimates are derived from the national manual for cost prices in the healthcare sector.[39] Unit cost estimates are combined with resource utilization data to obtain a net cost per patient over the entire follow-up period. Unit cost estimates are derived from the national manual for cost prices in the healthcare sector. Costs of reduced ability to work are estimated using the friction costs method. Treatment costs are calculated using activity-based-costing methods, thus measuring actual resources (time of therapist, time of patients, facilities) used. Unit cost estimates are combined with resource utilization data to obtain a net cost per patient over the entire follow-up period.

Quality of life

To measure the *health-related quality of life* of cancer patients, a validated health-related quality of life instrument is used, the EuroQol-5D (EQ-5D; [40]). The EQ-5D is a generic instrument comprising five domains: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. The EQ-5D index is obtained by applying predetermined weights to the five domains. This index gives a societal-based global quantification of the participant's health status on a scale ranging from 0 (death) to 1 (perfect health). Participants are also asked to rate their overall quality of life on a visual analogue scale (EQ- 5D VAS) consisting of a vertical line ranging from 0 (worst imaginable health status) to 100 (best imaginable). The EQ-5D is available in a validated Dutch translation.[41] Because there are indications that the Short Form-12 (SF-12; [42]), another questionnaire on health-related quality of life, is more sensitive to change in populations with less severe morbidity than the EQ-5D [43], the SF-12 is administered as well. The SF-12 consists of 12 items yielding two summary scores for physical and mental health. Scoring is norm based with a mean of 50 (SD = 10); higher scores indicate better health.

TABLE 2: MBCT curriculum content

Theme of session	Meditation exercise	Didactic teaching	Homework
1. The automatic pilot	• Body scan	• Intention of participating • Raisin exercise	• Bodyscan • Mindful eating • Mindful routine activity
2. Dealing with barriers	• Body scan	• Observation exercise "walking through the streets" • Mindfulness of the breath	• Bodyscan or mindfulness of the breath • Positive experiences diary • Mindful routine acitivity
3. Mindfulness of the breath	• Movement exercises lying down • Mindfulness of the breath and body	• 3-minutes breathing space	• Body scan or movement exercises • Negative experiences diary • 3-minute breathing space three times a day
4. Staying present	• Sitting meditation • Walking meditation	• Psycho-education "reacting/responding stress"	• Sitting meditation or walking meditation or movement exercises • Stress diary • 3-minute breathing space • Walking meditation
5. Allowing	• Sitting meditation • Walking meditation	• Psycho-education "anxiety, anger and depression, helping and non-helping thoughts"	• Sitting meditation • Mindful communication exercise • 3-minute breathing space • Walking meditation
6. Mindful communication	• Movement exercises standing up • 3-minute breathing space in stressful situations	• Psycho-education "communication" • Nonverbal (Aikido) and verbal (Deeply listening) communication exercises	• Sitting meditation, movement exercises or body scan • 3-minute breathing space • Walking meditation
Silence day	• Various exercises • Silent lunch and tea breaks		
7. Taking care of yourself	• Sitting meditation, open awareness • 3-minute breathing space	• Energy balance and relapse prevention	• Mindful exercise at will • Relapse prevention plan • 3-minute breathing space
8. From stress to inner strength	• Body scan	• Training evaluation and looking forward	

Effect predictors

Presence of DSM-IV Axis I mood/anxiety disorders is assessed by the SCID-I [44] which is a structured clinical interview. The interviewer rates answers on standardized questions during the interview on a scoring form. Subsequently, the presence or absence of symptoms is assessed. The SCID-I is administered by trained interviewers. An experienced psychiatrist (EBI) supervises the administration of the SCID-I. In the current study, neuroticism is assessed with the NEO Five Factor Inventory.[45] A shorter version of the Revised NEO Personality Inventory (NEO-PI-R), the NEO-FFI has 60 items (12 per domain) derived from the original 240 items. The five factor domains assessed by this measure are neuroticism, extraversion, openness to experience, agreeableness, and conscientiousness. The psychometric properties of the Dutch NEO-FFI are good.[46]

Process measures

Mindfulness skills

Mindfulness skills are assessed with the 24-item Five Facet Mindfulness Questionnaire Short Form (FFMQ-SF). The FFMQ consists of five subscales: observing, describing, acting with awareness, non-judging of inner experience and non-reactivity to inner experience. The FFMQ is sensitive to change in mindfulness-based interventions (e.g. [21]). A Dutch 24-item short form of the FFMQ (FFMQ-SF) was developed and assessed in a sample of 376 adults with clinically relevant symptoms of depression and anxiety and cross-validated in an independent sample of patients with fibromyalgia.[47] The FFMQ-SF was positively related to well-being and openness to experience and inversely related to measures of psychological symptoms, experiential avoidance, and neuroticism.

In addition, in both group and Internet-based MBCT the following process measures are administered at the start of each weekly session in order to determine processes of change during both interventions. In the group MBCT they are handed out in paper by the teacher, in the Internet-based MBCT intervention they are provided online at the beginning of a new training week. The Mindful Attention Awareness Scale (MAAS; [48]) is administered weekly to assess *mindful attention in daily life*. The MAAS has been shown to have an similar factor structure in cancer patients as in the general population.[49] Chronbach's alpha for the Dutch version ranged between .82 and .87.[50] Positive and negative affect is assessed weekly using the International Positive and Negative Affect Scale - Short Form I-PANAS-SF). The crosscultural factorial invariance, internal reliability, temporal stability, and convergent and criterion-related validities of the I-PANAS-SF were found to be acceptable.[51]

Working alliance

Working alliance is measured with a translated and shortened form of the Working Alliance Inventory (WAI; [52]), consisting of three subscales assessing: 1) how closely client and therapist agree on and are mutually engaged in the goals of treatment, 2) how closely client and therapist agree on how to reach the treatment goals, and 3) the degree of mutual trust, acceptance, and confidence between client and therapist. Patients score on a 5-point scale ranging from rarely to always.[53, 54] The 12-item inventory was validated in a Dutch-speaking sample and a recent study showed that internal consistency of the short form was >.80 for all separate subscales and .87 for the total.[55] The WAI is administered before session 2, 5 and 9.

Group cohesion

Self-reported group cohesion is assessed in the group MBCT condition with the Dutch Group Cohesion Questionnaire (GCQ) that has been used in cancer patients before.[56] The GCQ consists of four subscales: the bond with the group as whole, the bond with other members, cooperation within the group and the instrumental value of the group bond. Each item is rated from 1 (totally disagree) to 6 (totally agree). Internal consistency of all scales was reported to range from adequate to good (0.66–0.88).[57] The GCQ is administered before session 2, 5 and 9.

Adherence

Adherence is assessed during the entire treatment period with a calendar (both for group and Internet-based MBCT) on which participants fill out whether they adhere to both formal (e.g. the sitting meditation) and informal (e.g. 3-min breathing space) mindfulness exercises.

Semi-structured interviews

In order to more fully understand how interventions bring about change, it is important to complement quantitative research with qualitative research.[58] For this reason participants' views on barriers and facilitators of the Internet-based MBCT are explored in more detail by conducting semi-structured interviews in a purposive sample of participants in the trial.

Statistics

Sample size

Based on post treatment HADS scores within the routine outcome data of cancer patients who received mindfulness at the Helen Dowling Institute, we expected post treatment HADS scores of 10.6 (*SD*=6.4) in the MBCT interventions and 14.8 (*SD*=8.1) in the TAU

condition. In the power calculation we ignored the dependency caused by the therapy groups, which has been found in previous research to be small.[59] As we compare both group and Internet-based MBCT to TAU, we corrected the corresponding alpha level to 0.025. Assuming a power of 0.9, a sample size of 65 per condition is needed. Taking an estimated expected dropout rate of 15% in the group MBCT and TAU and 30% in the Internet-based MBCT into account, we aim to recruit 76 participants in the group MBCT and TAU conditions and 93 in the Internet-based MBCT, thus 245 patients in total.

Statistical analysis

All analyses are carried out using the intention to treat and per protocol samples. The primary analysis is aimed at showing superiority of group MBCT and Internet-based MBCT compared to TAU in terms of psychological distress directly post treatment in the intention to treat sample. Secondary analyses of the stability of the treatment effect are conducted using the data from the assessments at 3 and 9 months post-treatment, using linear mixed models to control for possible dependency caused by the repeated measurements.

We will use the bootstrapping procedure as it provides the most powerful and reasonable method of obtaining confidence limits for specific indirect effects under most conditions.[60] In all mediation analyses, post-treatment HADS scores are controlled for baseline HADS scores. Residual change scores for all potential mediators are calculated. [61] To explore whether the mediators (partly) affect the relation of condition on post-treatment symptom levels, the model including the potential mediators is compared with the model without mediators for both univariate and multivariate models. Subsequently, 95% bias corrected and accelerated confidence intervals (95% CI) [62] are calculated to explore the contribution of each individual mediator and the group of mediators in total.

Cost-effectiveness

The economic evaluation is based on the general principles of a cost-utility analysis and is performed alongside the clinical trial which compares three alternatives: 1) group MBCT; 2) Internet-based MBCT, and 3) TAU. Primary outcome measures for the economic evaluation are: costs (here we follow the Dutch guidelines for costing research [39]) and quality adjusted life years (QALY) measured by the EQ-5D. Secondary analyses will explore the possible differences in outcome with HrQoL measured by SF-12. The societal perspective is operationalised by including productivity losses/gains applying the friction cost method on a per patient basis by means of the TiC-P.[38]

The incremental cost-effectiveness ratio (ICER) "cost per Quality-Adjusted Life Year (QALY) gained" based on EQ-5D utilities according to the Dutch algorithm [41] is computed and uncertainty surrounding these parameters is determined using the bootstrap method (dealing with potential skewness in the distributions). A cost-effectiveness acceptability curve will be derived that is able to evaluate efficiency by using a range of thresholds (Willingness To Pay for a QALY gained). The impact of uncertainty surrounding relevant deterministic parameters on the ICER is subsequently explored using one-way sensitivity analyses on the range of extremes.

The cost analysis exists of two main parts. First, on patient level, volumes of care is measured using patient questionnaires. Per arm (intervention and control groups) full cost-prices are determined using activity based costing. The second part of the cost analysis consists of determining the cost prices for each volume of consumption in order to use these for multiplying the volumes registered for each participating patient. The Dutch guidelines for cost analyses are used with regard to prices.[39] For units of care/resources where no guideline or standard prices are available real cost prices are determined.

DISCUSSION

A significant proportion of cancer patients suffers from psychological distress and is in need of appropriate psychological treatment.[4] An increase in the number of patients who will have to deal with the consequences of having cancer is to be expected [2, 3], which calls for more widely accessible and effective psychosocial treatment. Mindfulness-based treatment has proven to be effective in reducing psychological distress in cancer patients.[8]

Providing Internet-based mindfulness could hold promise in terms of increasing accessibility: patients do not have to travel and treatment planning is more flexible in the light of individual circumstances. Therefore, the current trial investigates the effectiveness in reducing psychological distress of both group- and Internet-based MBCT compared to TAU.

Furthermore, although the need of cost-effectiveness evaluations of psycho-oncological interventions has long been recognized [63], information on the cost-effectiveness of mindfulness interventions is largely absent. In addition to the clinical effectiveness, the current trial also investigates cost-effectiveness of both group- and Internet-based

MBCT interventions compared to TAU. We hope that our trial provides further insight into the accessibility, effectiveness and cost-effectiveness of group and Internet-based MBCT in the reduction of psychological distress in patients with cancer.

LIST OF ABBREVIATIONS

TAU	Treatment as Usual
CBT	Cognitive Behavioral Therapy
ES	Effect Size
MBCT	Mindfulness-Based Cognitive Therapy
MBSR	Mindfulness-Based Stress Reduction
HADS	Hospital Anxiety and Depression Scale
MAAS	Mindful Attention and Awareness Scale
I-PANAS-SF	International Positive and Negative Affect Scale Short Form
SCID-I	Structural Clinical Interview for DSM-IV Axis I Disorders
TiC-P	and iMTA questionnaire for Costs associated with Psychiatric illnesses
MBI-TAC	Mindfulness-Based Interventions – Teacher Assessment Criteria
FCRI	Fear of Cancer Recurrence Inventory
MHC-SF	Mental Health Continuum – Short Form
EQ-5D	EuroQol-5 Dimensions
SF-12	Short-Form-12
NEO-FFI	NEO-Five Factor Inventory
NEO-PI-R	NEO-Personality Inventory-Revised
FFMQ-SF	Five Factor Mindfulness Questionnaire – Short Form
WAI	Working Alliance Inventory
GCQ	Group Cohesion Questionnaire
ICER	Incremental Cost Effectiveness Ratio
QALY	Quality Adjusted Life Year

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Chapter 4

Face-to-Face and Internet-Based Mindfulness-Based Cognitive Therapy Compared With Treatment as Usual in Reducing Psychological Distress in Patients With Cancer: A Multicenter Randomized Controlled Trial

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ABSTRACT

Purpose

Mindfulness-based cognitive therapy (MBCT) has been shown to alleviate psychological distress in patients with cancer. However, patients experience barriers to participating in face-to-face MBCT. Individual Internet-based MBCT (eMBCT) could be an alternative. The study aim was to compare MBCT and eMBCT with treatment as usual (TAU) for psychological distress in patients with cancer.

Patients and Methods

We obtained ethical and safety approval to include 245 patients with cancer with psychological distress (≥11 on the Hospital Anxiety and Depression Scale) in the study. They were randomly allocated to MBCT (*n*=77), eMBCT (*n*=90), or TAU (*n*=78). Patients completed baseline (T0) and postintervention (T1) assessments. The primary outcome was psychological distress on the Hospital Anxiety and Depression Scale. Secondary outcomes were psychiatric diagnosis, fear of cancer recurrence, rumination, health-related quality of life, mindfulness skills, and positive mental health. Continuous outcomes were analyzed using linear mixed modeling on the intention-to-treat sample. Because both interventions were compared with TAU, the type I error rate was set at $p<.025$.

Results

Compared with TAU, patients reported significantly less psychological distress after both MBCT (Cohen's *d*, .45; $p<.001$) and eMBCT (Cohen's *d*, .71; $p< .001$) . In addition, post-treatment prevalence of psychiatric diagnosis was lower with both MBCT (33% improvement; $p=.030$) and eMBCT (29% improvement; $p=.076$) in comparison with TAU (16%), but these changes were not statistically significant. Both interventions reduced fear of cancer recurrence and rumination, and increased mental health–related quality of life, mindfulness skills, and positive mental health compared with TAU (all *p*s , .025). Physical health–related quality of life did not improve ($p=.343$).

Conclusion

Compared with TAU, MBCT and eMBCT were similarly effective in reducing psychological distress in a sample of distressed heterogeneous patients with cancer.

INTRODUCTION

From 2025 onward, 20 million people worldwide will be diagnosed with cancer each year.[1] Approximately one third of patients with cancer suffer from significant psychological distress[2], resulting in reduced quality of life, decreased compliance with medical care, and prolonged duration of hospital stay.[3,4] The prevalence of psychiatric disorders in oncologic settings is 30% to 40%.[3] Effective and accessible interventions are needed to reduce psychological distress and psychiatric disorders in patients with cancer.

Mindfulness-based interventions (MBIs)[5,6] such as mindfulness-based cognitive therapy (MBCT) teach participants to be more mindful in daily life through meditation exercises, yoga, group discussions, and didactic teaching.[5] A 2012 meta-analysis of randomized controlled trials (RCTs) of MBIs in 955 patients with cancer found significant improvements in depressive and anxiety symptoms.[7] Since then, a number of RCTs have confirmed this.[8-13]

However, because MBIs typically require in-person attendance at classes over several weeks, many patients with cancer experience barriers to participation. These may include impairments due to illness and anticancer treatments, adverse effects that result in advice to avoid groups of people, or limited transportation options.[14] Consequently, uptake of face-to-face interventions for patients with cancer has been lower than, for instance, telephone- based interventions.[15]

In contrast, Internet-based interventions are easily accessible and save travelling time.[16] Therapist-guided Internet interventions have been shown to be effective for psychiatric and somatic conditions.[17] Although evidence for Internet-based MBIs (eMBIs) in cancer is scarce, one controlled study of 62 patients found that synchronous videoconferencing sessions led to significant improvements in mood, stress symptoms, and mindfulness skills.[18] In addition, an uncontrolled cohort of 257 fatigued patients showed significant improvements in fatigue and psychological distress after individual eMBCT.[19]

To date, no study has simultaneously compared the effectiveness of both MBCT and Internet-based MBCT (eMBCT) with treatment as usual (TAU). The primary aim of this RCT was to investigate whether MBCT and eMBCT were each superior to TAU in reducing psychological distress in a sample of distressed patients with cancer. Moreover, we hypothesized that there would be a reduction of psychiatric diagnoses, fear of cancer recurrence, and rumination, and an improvement in health-related quality of life, mindfulness skills, and positive mental health in both interventions compared with TAU.

We explored moderators of intervention dropout and outcome in the interventions: sex, age, cancer diagnosis, anticancer treatment intent, psychiatric diagnosis, neuroticism, and therapist.

PATIENTS AND METHODS

Trial Design

A three-armed multicenter, parallel group RCT was conducted to compare the effectiveness of MBCT and eMBCT with TAU in reducing psychological distress in patients with cancer. Anticipated dropout rates were 15% in MBCT and TAU, and 30% in eMBCT.[19] Given the anticipated dropout rates, the allocation ratio was 1:1.2:1. Patients randomly assigned to receive TAU were secondarily randomly assigned to MBCT or eMBCT, to be given after the TAU period of 3 months. The study was approved by the ethical review board of the Radboud University Medical Center (CMO Arnhem-Nijmegen 2013/542). All centers provided local ethics approval. The study was registered on Clinicaltrials.gov (NCT02138513) shortly afterthe start of recruitment and was reported following CONSORT guidelines.[20] A protocol article was published in advance of trial completion.[21]

Participants

Inclusion criteria were (1) a cancer diagnosis, any tumour type or stage, at any time, receiving or not receiving treatment; (2) a score of 11on the Hospital Anxiety and Depression Scale (HADS); (3) computer literacy and Internet access; (4) ability to participate in both MBCT and eMBCT; and (5) good command of the Dutch language. Exclusion criteria were (1) severe psychiatric morbidity, such as suicidal ideation and/or current psychosis; (2) change in psychotropic medication within a period of 3 months before baseline; and (3) previous participation in four or more sessions of an MBI.

Procedure

Patients were recruited from April 2014 to December 2015 via healthcare professionals in six centers (*n*=64; 26%) via online media (*n*=49; 20%), offline media (*n*=44; 18%), patient associations (*n*=43; 18%), and peers (*n*=27; 11%). Eighteen patients (7%) could not remember how they heard about the study. Interested patients filled out the HADS on the research Web site. Patients with HADS ≥11 received a phone call from one of the researchers, during which the remaining inclusion and exclusion criteria were assessed.

Once patients provided oral and written consent and had completed the baseline assessment, they were randomly assigned to MBCT, eMBCT, or TAU and informed about their allocation by E.B.

Intervention

Face-to-face MBCT

The MBCT protocol [6] was tailored to patients with cancer by including cancer-related psycho-education and adapted movement exercises. The MBCT consisted of eight weekly 2.5-hour group sessions, a 6-hour silent day, and daily home practice assignments guided by audio files. Each participant in both interventions received a folder with information on each session.

Internet-based Mindfulness-based cognitive therapy

The eMBCT was delivered individually and included weekly asynchronous written interaction with a therapist over e-mail. Patients were granted access to a secure Web site containing material for 8 weeks plus a silent day and an inbox. Each session included an introduction and daily meditation exercises with meditation audio files. Patients were asked to practice and fill out practice diaries on a daily basis. They were provided with (fictional) patients' descriptions to emphasize common experiences and clarify the use of the diaries. Patients were given written instructions after week 5 to prepare for their silent day at home. In the week of the silent day, patients were provided with a program similar to the MBCT silent day. At the end of the silent day, eMBCT patients wrote about their experiences in an essay. The therapist provided written feedback on the completed forms and the essay via the secured inbox on a prearranged day of the week. Having completed four or more sessions of MBCT was defined as a minimum adequate dose in both interventions.[22]

Treatment as usual

TAU consisted of all healthcare that patients usually received. Except for not participating in MBIs during the study period, there were no restrictions on healthcare utilization. Data on healthcare utilization were gathered using the Trimbos/iMTA questionnaire for Costs associated with Psychiatric illnesses.[23]

Therapists

Fourteen therapists participated: seven provided both interventions, two only provided MBCT, and five only provided eMBCT. All therapists fulfilled the criteria of the UK Mindfulness-Based Teacher Therapist Network Good Practice Guidelines for Teaching MBIs. [24] supervision meetings were held during the intervention phase of the trial.

All face-to-face MBCT sessions were videotaped to evaluate therapist competency using the Mindfulness-Based Interventions-Teachers Assessment Criteria.[25] Therapist competency levels were determined by two independent therapists who evaluated two random sessions from each of the nine therapists providing face-to-face MBCT (who treated 80.8% of all patients receiving either intervention). Interrater reliability was .72. Of the nine therapists rated, four were considered proficient (*n*=64 patients), three were considered competent (*n*=64 patients), and two were considered beginner (*n*=7 patients).

Measures

Primary outcome

Psychological *distress* was measured with the HADS, a 14-item self-report scale designed to assess anxiety and depression in medical outpatients.[26,27] It has good psychometric properties in the general medical population, including patients with cancer in palliative care.[28] The internal consistency in this sample was high (α = .87).

Secondary Outcomes

Psychiatric diagnosis was assessed by the SCID-I.[29] The SCID-I was administered by trained interviewers following or having completed a Master in Behavioral Science (FC), supervised by either an experienced psychiatrist (EB and AS) or psychologist (ML). All interviews were audio taped. *Fear of cancer* recurrence was assessed with the severity subscale of the Fear of Cancer Recurrence Inventory (FCRI).[30, 31] *Rumination* was measured by the rumination subscale of the Rumination and Reflection Questionnaire (RRQ)[32], *health-related quality of life* by the mental and physical scales of the Short-Form 12 (SF-12)[33] using Dutch norm scores from a clinical sample[34], *mindfulness skills* by the Five Facet Mindfulness Questionnaire Short Form (FFMQ-SF)[35] and *positive mental health* by the Mental Health Continuum-Short Form (MHC-SF).[36] As a potential moderator, *neuroticism* was measured by the Neuroticism Extraversion Openness-Five Factor Inventory (NEO-FFI).[37] Further details of the measures used are included in the study protocol.[21]

Sample size

The sample size calculation was based on previous post-intervention HADS scores of cancer patients who received MBCT at the Helen Dowling Institute (*M*=10.6, *SD*=6.4) compared to those who had not (*M*=14.8, *SD*=8.1). With 90% power, *n*=65 patients per condition were needed. Due to anticipated differential dropout rates between treatment arms, the recruitment target was *n*=245: *n*=76 in each of MBCT and TAU, and *n*=93 in eMBCT.

Randomization and blinding

Once patients provided oral and written consent and completed the baseline assessment, they were randomized to MBCT, eMBCT or TAU by a computer-generated allocation sequence designed by an independent biostatistician. This custom software was accessed by researcher EB via a study-specific website. Randomization was carried out with a fixed block size of sixteen stratified for region and minimized for sex, cancer diagnosis (breast vs. other) and anticancer treatment intent (curative vs. palliative). After randomization, EB informed patients of their allocation by email. EB planned and invited participants for the follow-up assessments, the standardised psychiatric interviews were conducted by FC and research assistants who were blind to treatment allocation. Both EB and FC instructed patients not to mention their treatment condition at the beginning of each psychiatric interview.

Statistical analysis

Statistical analyses were carried out using SPSS22 (IBM). Differences between conditions in demographic and clinical variables were tested by chi-square analysis and t-tests. Continuous outcomes were analyzed with linear mixed modeling in a model with uncorrelated residual errors and random intercepts, including group allocation and its interaction with time and stratification (region) and minimization (sex, cancer diagnosis, anticancer treatment intent) variables as fixed factors. Since both MBCT and eMBCT were compared to TAU, the two-sided type I error rate was corrected to .025 for the two direct (e)MBCT comparisons with TAU. All reported analyses used the Intent-To-Treat (ITT) sample. Missing continuous outcomes were imputed with Automatic Multiple Imputation (MI) on basis of linear regression (20 iterations). The multiple imputation-dataset was considered the primary dataset. Cohen's *d* effect size (ES) were calculated using post-intervention means and baseline pooled *SD*'s. These statistics are commonly used in psychological contexts to compare effect sizes across studies[38] and in accordance with Cohens' guidelines, Cohens's *d* effect sizes were interpreted as small (0.2 to 0.5), medium (0.5 to 0.8) or large (>0.8).[39]

In addition, the Reliable Change Index (RCI) was calculated by dividing the observed difference score by the standard error of measurement. Each participant was categorized as improved (RCI <-1.96), no change (-1.96 to 1.96) or deteriorated (RCI >1.96).[40] Improvements in terms of psychiatric diagnosis and RCI were assessed using chi-square analyses.

Exploratory moderation analyses of dropout were done using logistic regression including an interaction term between completer (yes/no) and possible moderators:

sex, age, cancer diagnosis, anticancer treatment intent, psychiatric diagnosis, neuroticism, and therapist. Exploratory moderation analyses of the primary outcome were done by including a three-way interaction term between condition, time and possible moderators: sex, age, cancer diagnosis, anticancer treatment intent, psychiatric diagnosis, neuroticism, and therapist. First, moderators were assessed in two separate analyses of either intervention compared to TAU. Second, moderators were assessed in analyses of the two intervention conditions only.

RESULTS

Study sample

In total, 532 patients were screened with the HADS (see Figure 1), of which 98 (18.4%) were excluded for scoring below 11. Of 434 patients who were contacted by telephone, 24 (5.5%) were excluded because of previous experience with mindfulness, 22 (5.1%) could not be contacted and 95 (21.9%) declined participation due to possible travelling distance (55, 12.7%), strong randomization preference (12 (2.8%), of which 4 had a preference for eMBCT and 8 for in-person group MBCT, and scheduling difficulties (11, 2.5%). Of the remaining 293 patients, another 10 (3.4%) could not be contacted and 38 (13.0%) declined participation after the baseline assessment. There were no significant differences in mean HADS scores between the 133 decliners (*M*=20.4, *SD*=5.6) and those who were randomized (*M*=20.6, *SD*=6.2). In total, 245 cancer patients were randomly assigned to MBCT (*n*=77), eMBCT (*n*=90) or TAU (*n*=78). The three conditions did not differ in terms of baseline demographic or clinical characteristics (see Table 1). The number of months between baseline and post-intervention assessments did not differ between MBCT (*M*=5.4, *SD*=2.3) and eMBCT (*M*=5.9, *SD*=1.8) (p =.13), but was higher in both intervention conditions than in TAU (*M*=3.5, *SD*=0.9) (p <.001).

Seventy out of 77 (90.9%) patients started MBCT and 71 (%) completed four or more sessions (*M*=7.9, *SD*=1.3) (see Figure 1). Eighty-two out of 90 (91.1%) patients started eMBCT and 71 completed four or more session (*M*=8.6, *SD*=12). The amount of estimated daily minutes of mindfulness practice did not differ significantly between MBCT (*n*=56, *M*=30.6, *SD*=26.0) and eMBCT (*n*=70, *M*=28.7, *SD*=29.3) (p = .69). Dropouts from the interventions were significantly higher in the eMBCT than in the MBCT group: ($\chi^2(1, n=167) = 3.92$, p = .047). Non-response on the post-treatment assessment was substantial (16.9% in MBCT, 16.7% in eMBCT and 10.3% in TAU) but did not differ significantly between conditions (p = .41). Non-responders were more often female (p=.033) and had less education (p=.037) than responders.

TABLE 1: Baseline Sociodemographic and Clinical Characteristics (*n*=245).

Characteristic	All *n*=245 n (%)	MBCT *n*=77 n (%)	eMBCT *n*=90 n (%)	TAU *n*=78 n (%)	*p*
Sex					.912
Female	210 (85.7)	67 (87.0)	77 (85.6)	66 (84.6)	
Male	35 (14.3)	10 (13.0)	13 (14.4)	12 (15.4)	
Age, years					.464
Mean	51.7	52.1	52.4	50.4	
SD	10.7	11.4	10.7	9.9	
Married / in a relationship					.491
Yes	202 (82.4)	65 (84.4)	76 (84.4)	61 (78.2)	
No	43 (17.6)	12 (15.6)	14 (15.6)	17 (21.8)	
Children					.314
Yes	169 (69.0)	48 (62.3)	65 (72.2)	56 (71.8)	
No	76 (31.0)	29 (37.7)	25 (27.8)	22 (28.2)	
Education					.451
High	166 (67.8)	54 (70.1)	56 (62.2)	56 (71.8)	
Middle	77 (31.4)	22 (28.6)	34 (37.8)	21(26.9)	
Low	2 (0.8)	1 (1.3)	0	1(1.3)	
Diagnosis					.724
Breast cancer	151 (61.6)	53 (68.8)	53(58.9)	45 (57.7)	
Gynecological cancer	18 (7.3)	2 (2.6)	9 (10.0)	7 (9.0)	
Prostate cancer	16 (6.5)	6 (7.8)	7 (7.8)	3 (3.8)	
Colon cancer	12 (4.9)	4 (5.2)	4 (4.4)	4 (5.1)	
Non-hodgkin's lymphoma	11 (4.5)	1 (1.3)	3 (3.3)	7 (9.0)	
Skin cancer	5 (2.0)	1 (1.3)	3 (3.3)	1 (1.3)	
Thyroid cancer	4 (1.6)	1 (1.3)	1 (1.1)	2 (2.6)	
Bladder cancer	4 (1.6)	1 (1.3)	2 (2.2)	1(1.3)	
Neuroendocrine tumour	4 (1.6)	1 (1.3)	2 (2.2)	1 (1.3)	
Other	20 (8.2)	7 (9.1)	6 (6.7)	7 (9.0)	
Years since diagnosis					.616
Mean	3.5	3.9	3.3	3.2	
SD	4.7	5.7	4.0	4.3	
Anticancer treatment intent					.472
Curative	206 (84.1)	68 (88.3)	74 (82.2)	64 (82.1)	
Palliative	39 (15.9)	9 (11.7)	16 (17.8)	14 (17.9)	

TABLE 1: Continued.

Characteristic	All *n*=245 n (%)	MBCT *n*=77 n (%)	eMBCT *n*=90 n (%)	TAU *n*=78 n (%)	*p*
Current treatment					.694
None	133 (53.1)	43 (55.8)	49 (54.4)	41 (52.6)	
Hormone therapy	79 (32.2)	22 (28.6)	28 (31.1)	29 (37.2)	
Combination of treatments	12 (4.9)	4 (5.2)	4 (4.4)	4 (5.1)	
Immunotherapy	9 (3.7)	1 (1.3)	5 (5.6)	3 (3.8)	
Radiotherapy	8 (3.3)	5 (6.5)	3 (3.3)	0	
Chemotherapy	4 (1.6)	2 (2.6)	1 (1.1)	1 (1.3)	

Healthcare Utilization

There were no significant differences in healthcare utilization between the intervention conditions and TAU (see Table 2) except for the proportion of patients receiving day-ward treatment (e.g. chemotherapy), which was higher in TAU.

Safety

A total of (*n*=21) (S)AEs unrelated to the intervention were reported in MBCT (*n*=6), in eMBCT (*n*=9) and TAU (*n*=6). One SAE occurred during the study period: a patient passed away after randomization due to illness.

Intervention outcomes

In between-group comparisons of both interventions compared with TAU, patients in the MBCT and eMBCT conditions reported significantly less psychological distress postintervention than did those receiving TAU, with small to medium effect sizes (Cohen's *d*, .45 and .71, respectively; Table 3; Figure 2). The proportion of patients demonstrating reliable improvement was significantly greater in MBCT than TAU (36% v 14%; χ^2 [1, *n*=134] = 8.44; *p*=.004) and in eMBCT than TAU (37% v 14%; χ^2 [1, *n* = 145] = 9.95; *p*=.002) (see Table 4). Improvement in rates of psychiatric diagnosis favored both interventions compared with TAU but were not statistically significant (MBCT: 32% v 16%; χ^2 [1, *n*=126] = 4.73; *p*=.030; and eMBCT: 29% v 16%; χ^2 [1, *n*=138] = 3.15; *p*=.076). Compared with TAU, both MBCT and eMBCT significantly reduced fear of cancer recurrence (Cohen's *d*, .27 and .53, respectively), rumination (Cohen's *d*, .42 and .51, respectively), and improved mental health–related quality of life (Cohen's *d*, .59 and .67, respectively), but not physical health–related quality of life (Cohen's *d*, .35 and .24, respectively). They also resulted in better mindfulness skills (Cohen's *d*, .47 and .82, respectively) and increased positive mental health compared with TAU (Cohen's *d*, .12 and .44, respectively).

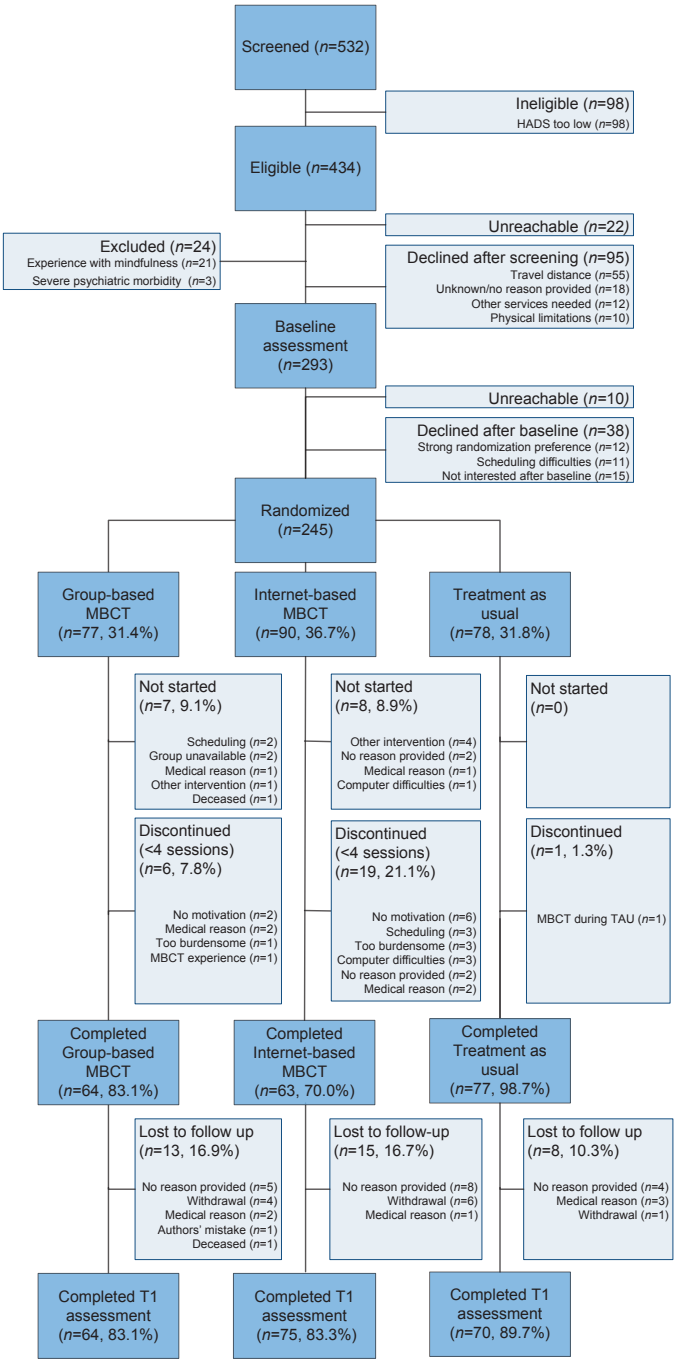

FIGURE 1. CONSORT diagram (*n*=245). HADS, Hospital Anxiety and Depression Scale; MBCT, mindfulness-based cognitive therapy; TAU, treatment as usual.

TABLE 2. Healthcare utilization during the intervention period for MBCT, eMBCT and TAU Groups

	All *n=198*		**MBCT *n*=63**		**eMBCT *n*=72**		**TAU *n*=63**		
	No.	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**	***p***
Hospital outpatient consultation	153	77	45	71	61	85	47	75	.153
Hospital overnight	13	7	4	9	4	6	5	8	.853
Hospital outpatient treatment	36	18	6	10	12	17	18	29	.02
Hospital ER	7	4	1	1	3	3	3	4	.588
Mental healthcare†	62	31	18	29	24	33	20	32	.834
General practitioner	116	59	35	56	39	54	42	67	.285
Physical therapist	92	47	29	46	40	56	23	37	.086
Complementary care	56	28	21	33	20	28	15	34	.491

Abbreviations: eMBCT, Internet-based MBCT; MBCT, mindfulness-based cognitive therapy; TAU, treatment as usual.
*Pearson χ 2 test. †Social worker, psychologist.

TABLE 3. Mean Scores at Baseline and Postintervention (both listwise deletion and pooled multiple imputation scores are depicted) and Between-Group Differences for Primary and Secondary Outcome Measures. *SE for imputed means

	Groups									Linear Mixed Modeling: Between-Group Differences							
	MBCT			eMBCT			TAU			P*	TAU-MBCT				TAU-eMBCT			
	n	M	SD*	*n*	M	SD*	*n*	M	SD*	Overall	Est.	SE	*p*	ES	Est.	SE	*p*	ES
Primary																		
HADS																		
T0	77	18.81	6.70	90	17.24	7.07	78	17.04	5.79									
T1 original	64	13.25	6.33	75	11.87	6.16	70	16.37	6.50	≤.001	4.65	1.00	≤.001	0.50	4.63	0.96	≤.001	0.70
T1 imputed	77	13.69	0.78	90	11.88	0.69	78	16.48	0.78	≤.001	4.56	1.02	≤.001	0.45	4.81	0.95	≤.001	0.71
Secondary																		
FCRI severity																		
T0	77	21.49	6.55	90	21.20	5.80	77	21.13	7.28									
T1 original	64	18.05	6.49	75	17.28	7.33	68	20.66	7.10	≤.001	2.27	0.86	0.009	0.38	3.34	0.82	≤.001	0.51
T1 imputed	77	18.65	0.79	90	17.06	0.81	78	20.53	0.84	≤.001	2.23	0.89	0.013	0.27	3.52	0.84	≤.001	0.53
RRQ rumination																		
T0	77	44.04	7.96	90	43.09	8.17	77	42.69	8.56									
T1 original	64	37.61	8.16	75	36.81	8.90	68	41.65	8.85	≤.001	4.87	1.14	≤.001	0.49	4.85	1.10	≤.001	0.58
T1 imputed	77	38.12	1.04	90	37.26	0.97	78	41.56	1.05	≤.001	4.77	1.2	≤.001	0.42	4.68	1.14	≤.001	0.51
SF-12 Mental																		
T0	77	32.48	10.19	90	34.50	12.15	78	34.74	11.10									
T1 original	64	43.41	9.67	72	44.17	9.95	63	36.78	11.31	≤.001	28.89	2.01	≤.001	0.62	27.88	1.95	≤.001	0.64
T1 imputed	77	42.71	1.23	90	44.25	1.210	78	36.42	0.95	≤.001	28.55	1.98	≤.001	0.59	28.07	1.92	≤.001	0.67
SF-12 Physical																		
T0	77	46.06	8.88	90	45.62	10.25	78	45.40	8.24									
T1 original	64	48.24	8.45	72	48.19	10.51	63	45.24	9.77	0.343	22.14	1.61	0.19	0.35	21.91	1.57	0.22	0.32
T1 imputed	77	48.43	1.11	90	47.60	1.20	78	45.40	1.21	0.05	22.38	1.61	0.14	0.35	21.99	1.57	0.21	0.24

TABLE 3. Continued.

	Groups									Linear Mixed Modeling: Between-Group Differences							
	MBCT			eMBCT			TAU			P*	TAU-MBCT				TAU-eMBCT			
	n	M	SD*	*n*	M	SD*	*n*	M	SD*	Overall	Est.	SE	*p*	ES	Est.	SE	*p*	ES
FFMQ-SF total																		
T0	77	72.43	9.69	90	76.39	10.87	77	75.75	11.18									
T1 original	64	82.02	10.42	75	85.52	11.94	70	77.26	11.80	≤.001	28.03	1.76	≤.001	0.45	28.06	1.69	≤.001	0.75
T1 imputed	77	81.61	1.29	90	85.75	11.33	78	76.73	11.41	≤.001	28.17	1.82	≤.001	0.47	28.35	1.70	≤.001	0.82
MHC-SF total																		
T0	77	34.05	12.39	90	37.16	13.77	77	37.56	12.46									
T1 original	64	40.02	12.39	75	43.53	13.14	70	37.86	13.34	0.001	25.19	1.71	0.003	0.17	26.10	1.64	≤.001	0.43
T1 imputed	77	38.85	1.51	90	43.13	1.46	78	37.36	1.59	≤.005	24.97	1.71	0.004	0.12	26.15	1.66	≤.001	0.44

TABLE 4: Clinically Significant Improvement Measured by Jacobson-Truax Reliable Change Index on HADS and Psychiatric Diagnosis Between Baseline and Postintervention for MBCT, eMBCT, and TAU Groups.

	Reliable change index (*n*=209)								Psychiatric diagnosis (*n*=202)							
	MBCT *n*=64			eMBCT *n*=75			TAU *n*=70		MBCT *n*=64			eMBCT *n*=76			TAU *n*=62	
	n	%	*p**	n	%	*p**	n	%	n	%	*p**	n	%	*p**	n	%
Improved	23	36	.004	28	37	.002	10	14	21	33	.030	22	29	.076	10	16
No change	39	61		47	63		54	77	34	67		50	66		49	79
Deteriorated	2	3	.184	0	0	.010	6	9	0	0	.075	4	5	.910	3	5

Moderation

Exploratory analyses yielded no significant moderation of intervention dropout or primary outcome in the analyses comparing both interventions to TAU separately (all *p*-values >.05), except for neuroticism. In the analyses comparing either MBCT interventions to TAU, there was a significant interaction between neuroticism and intervention condition (MBCT vs. TAU $p = .014$, eMBCT vs. TAU $p = .004$). Patient scoring higher on neuroticism on baseline improved more on psychological distress in both intervention conditions than in TAU.

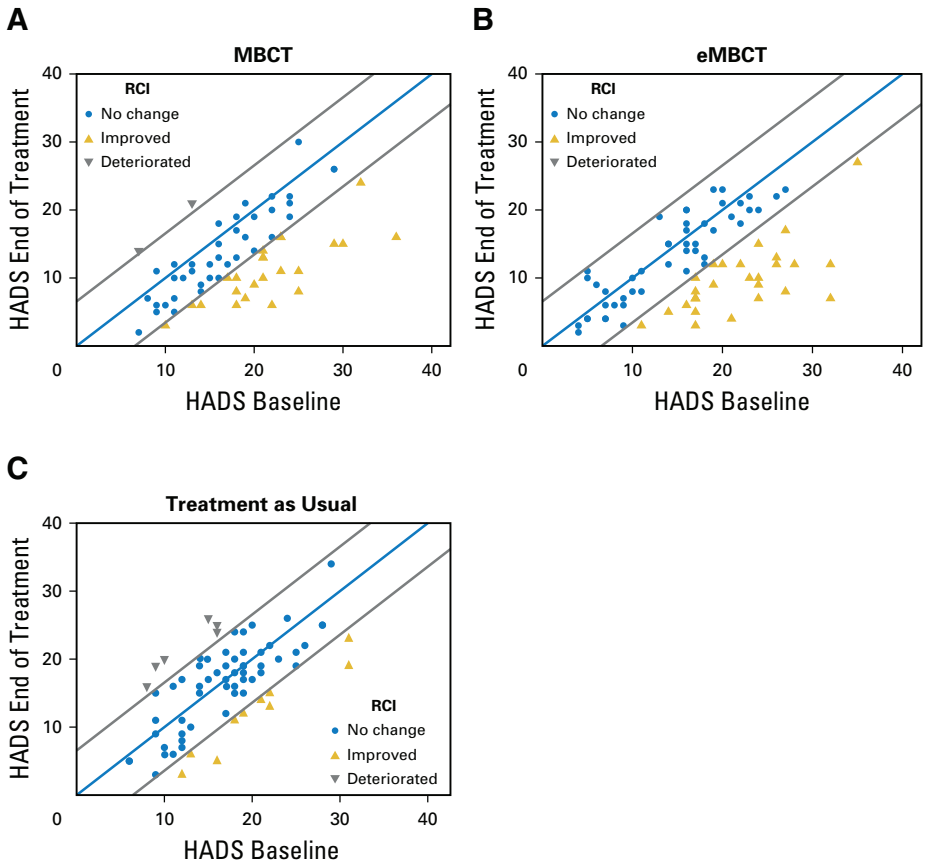

FIGURE 2. Change in Hospital Anxiety and Depression Scale (HADS) scores between baseline and postintervention for(A) mindulness-based cognitive therapy (MBCT), (B) Internet-based mindful-based cognitive therapy (eMBCT), and (C) treatment as usual (TAU) groups. The blue diagonal line represents no change in HADS between baseline and postintervention, and the gray upper and lower lines represent the upper (above indicates deteriorated) and lower (below indicates improved) bounds of the 95% CI of the Jacobson-Truax reliable change index (RCI).

DISCUSSION

To our knowledge, this is the first study to simultaneously compare MBCT and eMBCT with TAU in a large sample of distressed heterogeneous patients with cancer. Both MBCT and eMBCT resulted in a statistically significant and clinically reliable reduction of psychological distress compared with TAU. Both interventions demonstrated similar reductions of fear of cancer recurrence, rumination, and improvements in mental (but not physical) health–related quality of life, mindfulness skills, and positive mental health compared with TAU.

Our study confirms previous findings regarding the effectiveness of eMBIs for cancer patients.[14,19] Although the group-based setting is considered important for MBIs,[41] the current study suggests that individual guided eMBCT with limited teacher feedback is also effective, thus improving the accessibility of this intervention for cancer patients. However, eMBCT did result in higher dropout rates than MBCT. Exploratory analyses did not yield any moderators of intervention dropout. Further, possibly qualitative, research examining reasons for dropout is critical to improve efficacy of web-based interventions.[42]

A strength of the current study is the patient-centred nature of the recruitment across multiple regions as in previous research we encountered difficulties with consecutive sampling of patients in hospital outpatient settings.[43] Other strengths are that the interventions followed strict protocols, was delivered by qualified therapists, and therapist competency was rated by two independent, experienced therapists. We systematically collected data on healthcare utilization during the study. The study used a broad array of outcome measures, including both observer-rated interviews and self-report questionnaires.

In addition to these strengths, the study has some limitations. The study was not powered to directly compare or determine non-inferiority of eMBCT to MBCT, as this would have required a larger sample size. As with other psycho-oncology research, the majority of the patients were middle-aged breast cancer patients. Although this is in line with the characteristics of cancer patients seeking psychosocial support,[44] this might limit generalizability to patients with other types of cancer. As one inclusion criterion was the ability and willingness to attend both MBCT and eMBCT, the sampling frame for the current study was probably not representative of patients who would prefer eMBCT in clinical practice. As treatment preference is often positively correlated with treatment outcome,[45] we would expect that this RCT under- rather than over-estimated the effects of eMBCT.

In terms of research implications, long-term results should be gathered to examine the stability of effects. In addition, data on cost-utility of MBIs in cancer patients should be collected.[46] Internet interventions do not involve costs of transportation, travelling time, space, equipment, cleaning, and other overhead costs and thus could be more cost effective. Possible mediators of the effect, such as mindfulness skills or rumination, should be further investigated.[47,48] Moreover, mediation analyses could also examine possible differences in adherence in both MBCT and eMBCT.

In terms of clinical implications, implementation of eMBCT could make MBIs more accessible for cancer patients without having to compromise intervention efficacy. However, intervention dropout could possibly be improved by the delivery mode of eMBIs.[49] Qualitative work demonstrates that aspects such as the individual nature and the asynchronous interaction of the current eMBCT is helpful for some patients.[50]

Future studies should assess how different eMBCT designs (e.g. blended designs combining the advantages of face-to-face and Internet-based elements)[51] could further improve intervention accessibility, adherence and effectiveness.[50]

LIST OF ABBREVIATIONS

RCT	Randomized Controlled Trial
MBI	Mindfulness-based intervention
MBCT	Mindfulness-Based Cognitive Therapy
eMBI	Internet-Based Mindfulness-Based Intervention
TAU	Treatment As Usual
HADS	Hospital Anxiety and Depression Scale
eMBCT	Internet-based Mindfulness-based Cognitive Therapy
MBI:TAC	Mindfulness-Based Interventions: Teachers Assessment Criteria
FCRI	Fear of Cancer Recurrence Inventory
RRQ	Rumination Reflection Questionnaire
SF-12	Short Form-12
FFMQ-SF	Five Facet Mindfulness Questionnaire - Short Form
MHC-SF	Mental health Continuum - Short Form
NEO-FFI	Neuroticism-Extraversion-Openness Five-Factor Inventory
SCID-I	Structured Clinical Interview for DSM-IV-TR Axis I disorders
ITT	Intention to treat
MI	Multiple Imputation
RCI	Reliable Change Index
ES	Effect Size

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Chapter 5

Mindfulness-based cognitive therapy for cancer patients delivered via Internet: qualitative study of patient and therapist barriers and facilitators

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ABSTRACT

Background

The number of patients living with cancer is growing, and a substantial number of patients suffer from psychological distress. Mindfulness-based interventions (MBIs) seem effective in alleviating psychological distress. Unfortunately, several cancer patients find it difficult, if not impossible, to attend a group-based course. Internet-based MBIs (eMBIs) such as Internet-based mindfulness-based cognitive therapy (eMBCT) may offer solutions. However, it is yet to be studied what facilitators and barriers cancer patients experience during eMBCT.

Objective

This study aimed to explore facilitators and barriers of individual asynchronous therapist-assisted eMBCT as experienced by both patients and therapists.

Methods

Patients with heterogeneous cancer diagnoses suffering from psychological distress were offered eMBCT. This 9-week intervention mirrored the group-based MBCT protocol and included weekly asynchronous written therapist feedback. Patients were granted access to a website that contained the eMBCT protocol and a secured inbox, and they were asked to practice and fill out diaries on which the therapist provided feedback. In total, 31 patients participated in an individual posttreatment interview on experienced facilitators and barriers during eMBCT. Moreover, eight therapists were interviewed. The data were analyzed with qualitative content analysis to identify barriers and facilitators in eMBCT.

Results

Both patients and therapists mentioned four overarching themes as facilitators and barriers: treatment setting (the individual and Internet-based nature of the treatment), treatment format (how the treatment and its guidance were organized and delivered), role of the therapist, and individual patient characteristics.

Conclusions

The eMBCT provided flexibility in when, where, and how patients and therapists engage in MBCT. Future studies should assess how different eMBCT designs could further improve barriers that were found.

INTRODUCTION

Cancer poses a major psychological challenge for individuals. A meta-analysis of psychiatric disorder in oncological and hematological settings yielded a prevalence of psychiatric disorder of 30% to 40%.[1] In the coming decades, a great increase is expected in the number of people living with cancer.[2] This means that a growing number of cancer patients are in need of effective and accessible psychological treatment.

Mindfulness-based interventions (MBIs) such as mindfulness-based stress reduction (MBSR) [3] and mindfulness-based cognitive therapy (MBCT) [4], the latter more oriented toward those in need of clinical psychological treatment, could be viable intervention options for cancer patients. Mindfulness is defined as follows: "paying attention, on purpose, in the present moment and nonjudgmentally".[5] Its practice enables participants to recognize habitual, conditioned modes of reacting, and to make a radical shift in how they relate to their thoughts, feelings, and body sensations, as well as to outer circumstances [6], such as when coping with cancer.

Evidence for the effectiveness of MBIs for cancer patients has rapidly expanded. In 2015, an overview including six systematic reviews in heterogeneous cancer patients demonstrated significant small to moderate effects on various psychosocial outcomes in cancer patients.[7] In addition, studies confirmed these effects at longer-term follow-up.[8,9] Moreover, studies demonstrated that the effect of MBIs in breast cancer patients might be mediated by nonreactivity, reduced catastrophizing, and increased self-kindness.[10,11]

Notwithstanding the potential of MBIs, several cancer patients encounter practical and psychosocial barriers that hamper access and participation in psychological treatments such as MBIs. These barriers include cancer-related illness, fatigue, limited mobility or disability, limited transportation options, and time constraints.[12,13] Internet-based interventions, such as Internet-based MBIs (eMBIs), may offer solutions to these problems. Mobile MBI apps have already demonstrated their potential.[14] Internet-based interventions are easily accessible, available 24×7, save travelling time, and could be less costly.[15] Evidence of over 100 well-controlled trials suggests that Internet-based treatments can be as effective as group-based psychological treatments for a wide range of psychiatric and somatic conditions.[16]

Moreover, a previous review suggests that eMBIs may be helpful in alleviating symptom burden of patients with physical health conditions, particularly when the eMBI is

tailored to specific symptoms.[17] A total of 16 studies examining eMBIs for people with chronic physical health conditions were reviewed, of which two specifically targeted cancer patients.

A randomized controlled trial (RCT; *n*=62) investigated the quantitative feasibility of Internet-based MBSR for cancer patients (mindfulness-based cancer recovery [MBCR]).[13] The Internet-based MBCR (eMBCR) consisted of synchronous videoconferencing sessions. Feasibility targets for recruitment and adherence (5% response rate, 30% eligible, and 85% consented) were achieved, and patients considerably improved on mood disturbance, stress symptoms, spirituality, and acting with awareness in the Web-based group relative to waitlist controls. Results suggested that eMBCR led to improved energy while also inducing relaxation.[18] In addition, an uncontrolled cohort study (*n*=257) of severely fatigued cancer patients evaluated an Internet-based mindfulness-based cognitive therapy (eMBCT).[12] In total, 34.6% (89/257) of the patients showed clinically relevant improvement in fatigue severity and 61.8% (159/257) of the patients adhered to treatment. In sum, evidence for eMBIs in cancer is scarce, but the first results seem promising.

However, how to optimally deliver eMBIs remains unknown.[17] It is unclear whether either synchronous (real time, e.g., instant messageing or videoconferencing) or asynchronous (delayed, e.g., email or message boards) is to be preferred. Patients are supposed to engage in an experiential inquiry-based learning process together with the therapist in eMBIs [6], but it is unknown whether such an experiential inquiry-based learning process is at all possible in an asynchronous format. In addition, it is unclear whether either facilitated (guided) or self-directed eMBIs are to be preferred. It is argued that the therapists' capacity to embody qualities and attitudes of mindfulness in the process of teaching is vital for effective delivery of MBIs.[6] Guidance seems to be a beneficial feature of Internet-based interventions in general [19], and exploratory subgroup analyses of a systematic review indicated higher effect sizes of stress and mindfulness skills for guided than unguided eMBIs.[15] However, a previous review also provided some initial support for unguided eMBIs.[20]

In short, the question of which eMBI delivery format is preferable in terms of program adherence, mindfulness skills, and outcome improvement needs further investigation.[17]

Previously, a qualitative study has provided important perspectives for examining the user experience in an MBI. In a qualitative study of an eMBI for recurrent depression, patients identified aspects such as flexibility and reduced cost, as well as the need for

support in time management.[21] Qualitative information on how patients and their therapists experience eMBCT could identify barriers and facilitators, and inform us whether it is possible to design useful, user-friendly, and effective eMBIs for cancer patients and where to improve delivery mode and design if necessary and possible. Therefore, the aim of this study was to gain understanding of the experienced facilitators and barriers of asynchronically delivered eMBCT in a sample of heterogeneous cancer patients and their therapists.

METHODS

Study Population and Procedure

The patients of this study took part in a 3-armed trial on the (cost-) effectiveness of MBCT for distressed cancer patients (Clinicaltrials.gov no. NCT02138513).[22] Patients were randomized to either eMBCT, group-based MBCT, or treatment as usual. The RCT is described in more detail in a protocol paper.[22] Patients for this trial were mainly recruited via online media (26.9%, 66/245), patient associations (17.6%, 43/245), and participating mental healthcare centers (16.7%, 41/245). In total, 245 cancer patients with any tumour type and any stage of disease scoring 11 or higher on the Hospital Anxiety and Depression Scale were randomized. The local ethics committee approved this study (CMO Arnhem Nijmegen 2013/542).

Qualitative Assessments: Semistructured Interviews (Patients) and Focus Group (Therapists). Both patients randomized to eMBCT and their therapists were invited by the researcher to talk about the following questions:

- How did you experience the eMBCT?
- What facilitated and what impeded your participation in eMBCT?
- How did you experience the relationship with the therapist or patient?
- How would you improve the eMBCT?

The abovementioned questions were followed by specific probes. Questions were asked in an open nondirective manner, allowing participants to speak freely about their experiences. Patients were interviewed via telephone or in groups within 3 months after eMBCT treatment completion or dropout. Patients were purposefully sampled to gather an even distribution of completers versus noncompleters and breast cancer versus other tumour types. Patient interviews were conducted by FC and EJ. FC is a PhD student with an MSc degree in behavioral science with no prior experience in qualitative research. He was the trial coordinator for the larger RCT [22], and had

conducted baseline and posttreatment research interviews before inviting patients for the posttreatment interview. EJ is a psychologist and mindfulness teacher with an MSc degree in psychology with prior experience with qualitative research.

Therapists were invited for a focus group interview during the last plenary therapist supervision session approximately 3 months after completing the last MBCT. Both the patient interviews and therapist focus group started by explaining confidentiality and the explorative nature of the interview. AS and ML conducted the focus group interviews. AS is a professor of psychiatry in the role of principle investigator of the larger RCT [22], with experience in several qualitative research projects in MBIs. ML is a senior researcher and clinical psychologist in the role of principle investigator of the larger RCT [22], with experience in several qualitative research projects on MBIs.

Data Analysis

We used conventional qualitative content analysis to analyze the data in which coding categories are derived directly from the text data.[23] We used ATLAS.ti version 7.1 software (Scientific Software Development GmbH, Berlin, Germany). Analysis started as soon as the first interview was conducted and continued with each additional interview. Interviews were transcribed verbatim, and each transcript was coded by 2 independent researchers (FC and EJ) to identify facilitators and barriers. Coding was performed as closely related to the patient's words as possible to minimize subjectivity. After 5 interviews, FC and EJ compared codes with each other, and a common coding scheme was developed. Remaining transcripts were coded using this common coding scheme and earlier transcripts were recoded. New codes were added when data were encountered that did not fit in the existing coding scheme. After 12 interviews, a larger group of researchers (FC, EJ, MS, ML, and AS) discussed all data within the coding scheme. Some codes were combined during this process, whereas others were split in subcategories. After 31 interviews, no new codes were added and it was concluded that saturation had been reached. All codes referring to the same phenomenon were grouped in a hierarchical structure in subcategories, and subcategories in themes by FC and EJ. The group of researchers (FC, EJ, MS, ML, and AS) subsequently discussed this classification until reaching consensus.

Intervention and Therapists

The eMBCT was based on the MBCT protocol for recurrent depression published by Segal et al.[4] The content was adapted to cancer patients by particularly tailoring the psychoeducation (eg, manageing cancer-related fatigue, pain, fear of cancer recurrence, and effects of cancer on partner communication) and movement exercises to their needs.[24]

The eMBCT was mainly text-based and included asynchronous interaction with a therapist similar to the study of Bruggeman Everts et al.[12] Patients were granted access to a website divided into a workspace containing 9 sessions (8 weeks + 1 full-day silent retreat) and a secured inbox. The therapist initiated the eMBCT by sending a welcome message to the patient. When patients logged-in, they were presented with the overview of all information and assignments due for that week. Each session contained an introductory text, and daily formal (eg, sitting meditation) and informal exercises (eg, awareness of everyday activities) with guided audiotaped files and accompanying diaries. Sessions also contained other home practice such as the pleasant or unpleasant events' diary.

The eMBCT was performed individually. To demonstrate the rationale and possible obstacles of each exercise, patients were provided with experiences of other (fictional) patients. Patients were asked to practice and complete the diaries on a daily basis. The therapist provided written feedback on their progress via the secured inbox on a prearranged day of the week. Next week's session only became available after completing the previous session. Patients always had access to their therapist via the inbox. Patients and therapists were notified via their regular email when they received a message via the secured inbox.

We defined adherence as having attended ≥4 sessions. Therapists without prior eMBCT experience were provided with guidelines and were supervised by more experienced eMBCT therapists. See Table 1 for therapists' characteristics. All therapists fulfilled the advanced criteria of the Association of Mindfulness-based Teachers in The Netherlands and Flanders, which are in concordance with the UK Mindfulness-Based Teacher Trainer Network Good Practice Guidelines for teaching mindfulness-based courses.[25]

TABLE 1. Demographical characteristics of Internet-based Mindfulness-based Cognitive Therapy therapists.

Variable (*n*=8)	**Mean (SD)**	***n* (%)**
Age, years	55.50 (7.2)	
Gender, female		6 (75)
Years of experience in teaching MBCT[a]	8.75 (2.7)	
Prior experience with eMBCT[b]		4 (50)

[a]MBCT: mindfulness-based cognitive therapy.
[c]eMBCT: Internet-based mindfulness-based cognitive therapy.

RESULTS

Sample

Out of the 125 patients randomized to eMBCT, 45 were invited for a posttreatment interview. In total, 12 patients declined and 2 recordings failed. As a result, 31 interviews were used in the qualitative analysis. Interviews lasted from 5 to 25 min. Out of the patients interviewed, 14 had participated in 4 or more sessions of eMBCT, 10 had attended less than 4 sessions of eMBCT, and 7 had not started at all. See Table 2 for patient characteristics.

A total of 11 out of 12 eMBCT therapists were invited for a focus group interview after completion of all eMBCTs. Out of these 12 therapists, 7 therapists agreed to participate and 1 therapist agreed to provide an individual interview with FC for scheduling reasons. Therapists declined either because of having provided too few individual online treatments to share experiences (*n*=1) or because of scheduling reasons (*n*=2). The focus group interview lasted for 90 min. The single individual therapist interview lasted for 25 min. The final sample of therapists included both therapists who had experience with online mindfulness before this project (*n*=4) and therapists who had no prior experience with online mindfulness before this project (*n*=4). See Table 2 for therapist characteristics.

All patient facilitators (Textbox 1), patient barriers (Textbox 2), therapist facilitators (Textbox 3), and therapist barriers (Textbox 4) could be divided into the following four themes: treatment setting, treatment format, role of the therapist, and patient characteristics. First, patients' facilitators and barriers are presented per each theme. Then, therapists' facilitators and barriers are presented per each theme.

TABLE 2. Demographic and clinical characteristics of Internet-based Mindfulness-based Cognitive Therapy patients.

Variable (*n*=31)	Mean (SD)	*n* (%)
Age, years	53.0 (12.3)	
Gender, male		6 (19)
Education level		
Secondary		14 (45)
Vocational or university		17 (55)
Time since diagnosis	3.2 (2.7)	
Cancer diagnosis		
Breast		16 (52)
Other		15 (48)
Cancer treatment intent		
Curative		24 (77)
Active cancer treatment		
Yes		11 (35)
Psychological distress, HADS[a]	16.2 (7.1)	
MBCT[b] adherence		
Completer		14 (45)
Dropouts		10 (32)
Other priorities		4 (40)
Too difficult		3 (30)
Too intensive		1 (10)
Illness		1 (10)
Missed peers		1 (10)
No start		7 (23)
Wanted MBCT		3 (43)
Illness		1 (14)
Other priorities		1 (14)
Could not log in		1 (14)
Needed mental health services		1 (14)

[a]HADS: Hospital Anxiety and Depression Scale. [b]MBCT: mindfulness-based cognitive therapy.

PATIENTS

Facilitators and barriers experienced by patients are depicted in Textboxes 1 and 2.

TEXTBOX 1. Patient facilitators across four themes and subthemes.

Patient facilitators

- Theme 1: treatment setting
  - Time management
    - Program at own time improves receptivity
  - Individual setting
    - Sense of autonomy
    - Not having to cope with other patients' stories
  - Home setting
    - Not having to travel
- Theme 2: treatment format
  - Website
    - Clear and easy to navigate
    - Privacy precautions
  - Diaries
    - Rereading own notes
    - Stimulated reflection
- Theme 3: role of the therapist
  - Practical guidance
    - Clarifying practical matters
  - Mindfulness
    - Deepened understanding
    - Embodiment stimulated practice
- Theme 4: patient characteristics
  - Writing fluency
    - Written expression in describing experiences
  - Curiosity
    - Curiosity stimulated perseverance

Patient Theme 1: Treatment Setting—Facilitators

Treatment setting concerned subthemes on the external conditions of the eMBCT: flexibility of timing, the individual nature, and the home practice environment of the training.

Time Management

It was considered convenient to be able to manage your own time schedule, which increased treatment receptivity. One patient stated the following:

Because you can start when you are ready and have the peace of mind for it, you can absorb it much better, because you actually want to at that moment. [Female breast cancer patient (curative), 65 years, completer]

TEXTBOX 2. Patient barriers across four themes and subthemes.

Patient barriers

- Theme 1: treatment setting
  - Time management
    - Responsibility for time management
  - Individual setting
    - No learning from peer group
  - Home setting
    - Lack of privacy in own home
  - Illness barriers
    - Cancer-related reading impairments
  - Lack of information
    - Lack of information before start
- Theme 2: treatment format
  - Website
    - Complicated
  - Diaries
    - Complicated to fill out
    - Obligatory nature was burdensome
    - Describing experiences was confrontational
- Theme 3: role of the therapist
  - Asynchronicity
    - No dialogue emerging
  - Frequency
    - Wished more frequent feedback
- Theme 4: patient characteristics
  - Writing fluency
    - Lack of verbal fluency made diaries difficult

Individual Setting

A patient indicated that the individual setting facilitated a sense of autonomy that helped in taking care of himself:

I didn't feel like doing the movement exercises. In a group setting I would have had to explain myself, so you are more inclined to go along with the group. But now, being on my own, I carried full responsibility for my own actions. Getting this space felt

comfortable, because there were moments at which the therapy really asked a lot of me. At those times I could allow myself to take a time out and decide when I wanted to continue again. [Male prostate cancer patient (palliative), 65 years, completer]

Furthermore, it was considered to be facilitating not to be confronted with other patients' cancer stories. One patient stated the following:

This only was about me and I didn't have to spend energy on someone else's story. [Female breast cancer patient (curative), 27 years, completer]

Home Setting

Being able to complete the sessions and exercises in your own home environment and not having to travel was appreciated. One patient stated:

For me, it was ideal because I knew that the group-based MBCT would take place at [the mental health institute] and it was impossible to reach by public transport. [Female breast cancer patient (curative), 27 years, completer]

Patient Theme 1: Treatment Setting—Barriers

Time Management

Responsibility for your own time management was mentioned as a barrier because it required a lot of self-discipline. One patient stated:

What I like about it is that I can manage my own time which went very well the first couple of weeks. After a while some chores interrupted me and then at the end of the day I realized: I still have to practice. Sometimes I did not do it anymore and sometimes I did. So you have to be very disciplined to stick to the schedule. [Female cervical cancer patient (curative), 46 years, completer]

Individual Setting

Patients described the lack of a group setting as a drawback of the intervention. They missed the peer support and the ability to learn together in the eMBCT. One patient stated:

I am a rational being. In a group there are always others who help me to unravel my emotions. This helps me. And I know, when I sit behind my computer my autopilot turns on and the treatment becomes a rational, experimental exercise. [Female breast cancer patient (curative), 54 years, no start]

Home Setting

Other patients mentioned that they felt less comfortable having to do exercises at home, not having the privacy they needed. One patient stated:

> *I practiced in my home office, but that room is connected to my living room. I found it uncomfortable to practice with my husband around, and even though he would never be eavesdropping, I felt restricted in doing certain exercises. [Female colon cancer patient (curative), 60 years, completer]*

Illness Barriers

One patient indicated that her cancer type caused her to have trouble reading. As the eMBCT was mainly text-based, this was a problem to her. She stated the following:

> *It was mainly physical, I didn't have the energy and my vision is in such a bad state. Even with medication, my vision is bad. And my eyes itch and burn and hurt. [Female bone marrow cancer patient (palliative), 55 years, no start]*

Lack of Information

Moreover, patients indicated that they would have wished more information on the way the platform and course were organized before the start of the training. One patient stated:

> *Expectation management would have helped a lot, I had a very brief instruction. And I have to choose where to put my energy into. What is expected of me, can I handle it, does it fit in my planning? [Female breast cancer patient (curative), 54 years, no start]*

Patient Theme 2: Treatment Format—Facilitators

The treatment format theme included codes on the facilitators and barriers of the means by which the eMBCT was internally organized and delivered.

Website

The website was accessible and navigating throughout the website was easy. One patient stated:

> *Opening the exercises and the way [the website] guided you through the structure was easy. [Male skin cancer patient (curative), 61 years, completer]*

Moreover, patients valued the privacy precautions and indicated that the website felt safe. One patient stated:

I thought it was neat that I could see who visited my profile. In my case it was only my therapist according to the system, so I presume that the system is right, but it felt well taken care of. [Female melanoma patient (curative), 33 years, completer]

Diaries

The diaries proved to be of value for patients because it enabled them to read back and learn from their own experiences. One patient stated:

In my own [diaries] I looked back to see what my experiences were yesterday, or how did I handle this last time? [Female melanoma patient (curative), 33 years, completer]

Patients also indicated that having to write stimulated reflection upon experiences. One patient stated:

Writing about my feelings was different from when I would have talked about it. It was more reflective, less spontaneous. I noticed that when I mailed I checked it again and again and added a few things. This really was an advantage. It really made me think about what I felt and experienced. Because of the writing itself this really hit me. [Female breast cancer patient (curative), 61 years, dropout]

Patient Theme 2: Treatment Format—Barriers

Website

The website was complicated to some patients. One patient stated:

The website and its explanation was not really user friendly. There were many steps you had to take before you could do what you actually had to do. [Female breast cancer patient (palliative), 49 years, dropout]

Diaries

A patient mentioned that the diaries were complicated to fill out:

I got the message that some fields still needed to be filled out. In general, I couldn't find where to fill out what in the diaries and it made me quit. [Male prostate cancer patient (palliative), 78 years, dropout]

Patients thought it was burdensome that the diaries were obligatory. One patient stated:

It was so much. Filling out the diaries every day […]. I subscribed for a mindfulness course because I didn't feel well and all of a sudden, you have this huge obligation. [Male palate cancer patient (curative), 30 years, dropout]

The diaries were also considered quite confronting at times. One patient stated:

When you had a negative experience, filling out the diary made me revive the negative moment. [Female cervical cancer patient (curative), 50 years, dropout]

Patient Theme 3: Role of the Therapist—Facilitators

This theme included codes on the role of the therapist and the way the therapist facilitated or hindered participating in eMBCT.

Practical Guidance

Patients indicated that the therapist was often able to clarify practical aspects that were unclear. One patient stated:

I always want to do things right, and I wasn't sure about how I did the meditation exercises in the beginning. Is this the way I am supposed to do this? So after a while I just mailed my therapist asking questions about the how and what of exercises, and I got a prompt reply most of the times.
[Female melanoma patient (curative), 33 years, completer]

Mindfulness

The ways in which therapists provided feedback enriched patients' understanding of underlying mindfulness values, such as the mild and nonjudgmental attitude. One patient stated:

(My therapist) was very patient and gave me all the space I needed […]. She was like this all the time, in everything she did, not forcing, but stimulating me. "Do it for yourself when you do the exercises. If you do them, you could benefit a lot." This made me feel more connected. [Female breast cancer patient (curative), 52 years, completer]

The embodiment of mindfulness values, such as the nonjudgmental attitude, supported and motivated patients to practice with the right intentions. One patient stated:

My therapist struck me as very mild. "Don't force yourself, be gentle," that certainly stood out. I don't know how she would have been if I hadn't practiced as much, but she was gentle with me. [Female melanoma patient (curative), 33 years, completer]

Patient Theme 3: Role of the Therapist—Barriers

Asynchronicity

The asynchronous nature of the feedback proved to be a barrier. According to the patient, the written feedback of therapist did not seem to encourage a dialogue but rather seemed limited to giving responses to questions. One patient stated:

> *Suppose I tell you I found the exercise uncomfortable. I then send you a message saying "I found it uncomfortable." Only after 3 days I then get a reply "What was uncomfortable? Can you specify what you mean?" I then specify what I mean in another message. You keep sending messages back and forth over a period of time. If you have a conversation with someone, you have direct interaction. It is a totally different mode of communication. In a business context I think messageing is fine. In this context it was unhelpful. [Female breast cancer patient (curative), 56 years, dropout]*

Frequency

As the therapist provided feedback on past weeks' diaries, sometimes questions were left unanswered for a whole week. Some patients would have liked to have more frequent feedback. One patient stated:

> *Just two three times a week a brief moment of contact saying "how are you"? [Female cervical cancer patient (curative), 50 years, dropout]*

Patient Theme 4: Patient Characteristics—Facilitators

Individual characteristics seemed to influence the fit between patient and eMBCT.

Writing Fluency

The ability to express themselves in writing was very helpful for some to give words to their subjective experiences and to ask for clarification to the therapist if it was necessary. One patient stated:

> *I am an easy writer, which perhaps set my experience apart from others. I can imagine that if you have a hard time expressing what you do and feel it would be different. [Female breast cancer patient (curative), 61 years, dropout]*

Curiosity

Curiosity sparked some to look beyond initial difficulties and to persevere in times of lack of motivation. One patient stated:

I think I was curious about the coming exercises. Maybe those will be more pleasant to do. This made me continue for a few more weeks. [Female colon cancer patient (curative), 60 years, completer]

Patient Theme 4: Patient Characteristics—Barriers

Writing Fluency

The heavy reliance on writing skills was a barrier to some patients. One patient stated:

I liked doing the exercises, but having to write down my experiences on a daily basis […], to sit down and write it all down, it put me off. For whom am I doing this? [Female breast cancer patient (curative), 51 years, completer]

THERAPISTS

Facilitators and barriers experienced by therapists are depicted in Textboxes 3 and 4.

TEXTBOX 3. Therapist facilitators across four themes and their subthemes.

Therapist facilitators

- Theme 1: treatment setting
  - Timing
    - Flexibility
  - Individual setting
    - Tailoring to patient
    - Better suited to some patients
- Theme 2: treatment format
  - Asynchronicity
    - More time for reflection
  - Schedule
    - Maintaining a schedule prevents dropout
  - Writing
    - Stimulated reflection
    - Becomes more goal oriented
  - Anonymity
    - Stimulates openness
- Theme 3: role of the therapist
  - Feedback
    - Providing group context
    - Provides reassurance
    - Personalizing training
- Theme 4: patient characteristics
  - Self-discipline
    - Supporting self-sufficiency

TEXTBOX 4. Therapist barriers across four themes and their subthemes.

Therapist barriers

- Theme 1: treatment setting
  - Timing
    - Larger time investment
    - More flexibility warranted
  - Individual setting
    - No modeling by peers
    - Elaboration on personal themes
- Theme 2: treatment format
  - Asynchronicity
    - No present moment experiences
    - Difficulty to maintain continuity
  - Technical issues
    - Technical issues cause delay
  - Writing
    - No nonverbal communication
    - Limited in therapeutical repertoire
    - Lack of understanding not readily apparent
- Theme 3: role of the therapist
  - Feedback
    - Empty diaries impair feedback
    - More explicit checking and self-disclosure necessary
  - Mindfulness
    - Embodying behind computer
- Theme 4: patient characteristics
  - Self-efficacy
    - Lack of self-efficacy
  - Writing fluency
    - Lack of ability in written expression

Therapist Theme 1: Treatment Setting—Facilitators

Timing

Therapists welcomed the fact in that they were able to choose at what time to provide feedback, which made them adaptive to circumstances. One therapist stated:

> *You can provide feedback in between other chores. Sometimes you plan to give feedback from 9 to 10 and then someone enters your office. There goes your planning. I then tell myself […] "I'll have time at another moment." This is an advantage, you can do it in your own time. [Female MBCT therapist, 60 years, 6 years of experience, prior eMBCT experience]*

Individual Setting

The individual nature of eMBCT allowed for tailoring to the patients' specific circumstances and giving feedback on individual real-life examples, which increases the relevance of the feedback. One therapist stated:

> *In the group you only have limited amount of time during which you must touch upon the most important themes. Online I have much more choice where to provide feedback on, what it means for a specific patient to react on autopilot, and which personal themes emerge. [Male MBCT therapist, 40 years, 10 years of experience, prior eMBCT experience]*

Another important advantage of the individual nature of eMBCT is that it can be provided to patients who may otherwise be unsuitable for the group. Another therapist stated:

> *Some patients can be so disruptive in a group. They don't get the point and only tell their own story. Sometimes you actually wished to provide someone in a group with an individual online training so you can address the individual themes. [Female MBCT therapist, 60 years, 6 years of experience, prior eMBCT experience]*

Therapist Theme 1: Treatment Setting—Barriers

Timing

Therapists indicated that providing feedback costs a considerable amount of time, which made it difficult for them to stick to a fixed time window. One therapist stated:

> *Especially in the beginning, it took me much longer. Because of asking questions, or clarifying issues. Or referring back to earlier diary entries. [Female MBCT therapist, 54 years, 12 years of experience, no prior eMBCT experience]*

Furthermore, therapists indicated that working online required much more flexibility and resulted in fragmentation of the times spent on eMBCT. One therapist stated:

> *When a patient indicates that the programme does not work, I start looking for help immediately. Even though I receive this mail outside of the time window for feedback. [Female MBCT therapist, 60 years, 6 years of experience, prior eMBCT experience]*

Individual Setting

Learning from fellow peer experiences in a group setting can be very helpful, and therapists felt limited in bringing in peer experiences themselves. One therapist stated:

> *In one-on-one contact, you can bring in experiences from other patients but to really experience them first hand provides another perspective. [Female MBCT therapist, 58 years, 11 years of experience, prior eMBCT experience]*

Moreover, it was often difficult to find the balance between elaboration on personal themes and the eMBCT theme. One therapist stated:

> *A tension emerged between someone's personal themes and combining those with this week's mindfulness theme. Sometimes I thought, "this patient is occupied by something entirely different." [Female MBCT therapist, 54 years, 5 years of experience, no prior eMBCT experience]*

Therapist Theme 2: Treatment Format—Facilitators

Asynchronicity

Therapists and patients interacted asynchronically. This meant that according to the therapists, patients had time for reflection. One therapist stated:

> *Because there is some time between practice and feedback some experiences get the time to settle in. Patients can think about it, read it again, check with themselves what they experienced and how they reacted to it. This time in between could perhaps engage patients. [Female MBCT therapist, 60 years, 6 years of experience, prior eMBCT experience]*

Moreover, the asynchronous contact was beneficial to therapists. One therapist stated:

> *Sometimes my irritation causes me to cut patients off. Behind the computer I can tell myself "let's put this to a rest for now." [Female MBCT therapist, 54 years, 5 years of experience, no prior eMBCT experience]*

Schedule

Maintaining a fixed interaction schedule between therapist and patient was very helpful in preventing treatment dropout. One therapist stated:

> *When patients are able to put in work on a weekly basis and we stick to this rhythm, a kind of synchronicity emerges and assignments and my feedback to these assignments flow naturally. [Female MBCT therapist, 62 years, 10 years of experience, no prior eMBCT experience]*

Writing

Writing feedback stimulated contemplation in therapists themselves. One therapist stated:

> *By taking a step back I recognized, hey, it annoys me what patients write down. Or I thought by myself, "come on, start practicing." Then I thought, "stop." You can read back your own feedback and then think by yourself "I should not do this." [Female MBCT therapist, 54 years, 5 years of experience, no prior eMBCT experience]*

Due to increasing experience, they got more efficient in their feedback over time. One therapist stated:

> *I became a lot more economical in my feedback over time. I tend to scan more for abnormalities or diary entries which I don't recognize, or diary entries of which I think "this could influence dropout." I tend to reply less, but what I say is then more relevant. [Male MBCT therapist, 40 years, 10 years of experience, prior eMBCT experience]*

Anonymity

The fact that patients were able to write about their experiences rather anonymously was helpful in opening up to experiences, which meant that in general, they shared their experiences in rather great detail. Moreover, it rendered the therapist to use patients' own quotes. One therapist stated:

> *Patients think I don't see them and they don't see me. They tend to confide more to a diary. Sometimes they told me "I don't know whether I should write everything down in such an uncensored manner." And I encouraged them to do so. I sometimes used quotes from their own diaries and they asked me "Wow, did I write this down?" They sometimes used impressive words.*
> *[Female MBCT therapist, 54 years, 5 years of experience, no prior eMBCT experience]*

Therapist Theme 2: Treatment Format—Barriers

Asynchronicity

Therapists were unable to comment on present moment experiences. This made it difficult to communicate what mindfulness is about. One therapist stated:

> *The experience-driven nature, the contact when a patient says something or shows emotion with which you can work instantly, which everyone immediately feels, that is*

direct. And it has a lot of impact. This is why things are so slowed down in the online. You have no direct experience to work with. [Female MBCT therapist, 54 years, 11 years of experience, no prior eMBCT experience]

The asynchronicity made it more difficult to maintain continuity and to prevent dropout from the eMBCT. One therapist stated:

Whenever a life event took place or I fell ill myself […] the schedule started to get awry fairly quickly. Patients hand in their diaries too late […] and you start hopping from miscommunication to miscommunication. In the worst case, the training gets bogged down and the output is zero. [Female MBCT therapist, 62 years, 10 years of experience, no prior eMBCT experience]

Technical Issues

Therapists indicated that technical issues also proved to be a barrier to treatment continuity. One therapist stated:

The technical background might have been a possible reason for dropout. I thought it was difficult myself. The whole logistics of where to find what, how the site was built up, where I had to click. I didn't think it was intuitive. It took me some time. [Female MBCT therapist, 54 years, 11 years of experience, no prior eMBCT experience]

Writing

Therapists indicated that a major drawback of the communication in writing is the complete lack of nonverbal communication. One therapist stated:

I prefer to see someone's nonverbal emotions. And to show that I open up. I had to think about this, how do I do this in writing? Is that even possible? [Female MBCT therapist, 58 years, 11 years of experience, prior eMBCT experience]

Moreover, they sometimes felt as if their therapeutical repertoire was limited by writing. One therapist stated:

I noticed that my feedback sometimes, as it was in writing only, did not contain everything I wanted to say. My repertoire is bigger and I was not always able to use all my skills. [Female MBCT therapist, 62 years, 10 years of experience, no prior eMBCT experience]

Sometimes, because of emphasis on reading and writing, it only became clear at a later stage that the patient did not fully understand everything. One therapist stated:

Sometimes patients come up with issues that have been taken care of already. Maybe because the training relies so heavily on reading and writing, patients absorb the training differently. [Female MBCT therapist, 49 years, 6 years of experience, no prior eMBCT experience]

Therapist Theme 3: Role of the Therapist—Facilitators

Feedback

Therapists indicated that it was facilitating for patients that they were able to provide a group context. One therapist stated:

You can provide examples from other patients or a funny example from a group situation. [Female MBCT therapist, 60 years, 6 years of experience, prior eMBCT experience]

In their feedback, they considered it motivating to provide reassurance very explicitly. One therapist stated:

In the online training I am much more complimentary for doing the exercises despite being so tired, and in the group I am much less inclined to do so. [Female MBCT therapist, 60 years, 6 years of experience, prior eMBCT experience]

Therapists were also involved in making the training more personal. One therapist stated:

I make it very clear from the start that "I write this feedback to you. This is not standardized feedback," so the patient knows he or she is dealing with an actual person. Someone actually replied "Good to know that there is a person at the other side." [Female MBCT therapist, 54 years, 5 years of experience, no prior eMBCT experience]

Therapist Theme 3: Role of the Therapist—Barriers

Feedback

A lack of diary entries was a turnoff for therapists in providing stimulating feedback. One therapist stated:

I noticed that it was not very stimulating when patients filled out very little. I think my own feedback will have been much shorter as well, and I much easier reverted to saying "good luck next week." [Male MBCT therapist, 40 years, 10 years of experience, prior eMBCT experience]

Therapists indicated that they experienced it as a barrier that more explicit disclosure and checking with the patient is necessary. One therapist stated:

> *I tell more about myself, "I recognize this when doing the body scan myself," far more often than I used to do in a group setting, and you have to be very explicit, check and check again how things come across. [Female MBCT therapist, 58 years, 11 years of experience, prior eMBCT experience]*

Mindfulness

Therapists also stated that it was hard for them to embody mindfulness values behind the computer. One therapist stated:

> *When patients start to get doubtful, or skeptical about the training, the power of your presence can be really important. Not in the sense of being able to convince people but with a visible nonverbal way of saying, "everything is OK," and showing this by being embodied. You can't do this via the PC. [Female MBCT therapist, 62 years, 10 years of experience, no prior eMBCT experience]*

Therapist Theme 4: Patient Characteristics—Facilitators

Self-Discipline

Therapists indicated that for some patients, the eMBCT was partly a training in self-discipline, which supported patients' self-sufficiency after the training. One therapist stated:

> *Some patients train in self-discipline. They have to, which maybe renders them more likely to continue practicing. Yes, dropout is higher, but those who do finish the training are very disciplined in doing so and did it more on their own, without the group context. More self-reliant, which is in line with mindfulness. [Female MBCT therapist, 54 years, 5 years of experience, no prior eMBCT experience]*

Therapist Theme 4: Patient Characteristics—Barriers

Self-Efficacy

In the eMBCT, patients need to be resolute and determined. This was mentioned as a barrier to complete eMBCT. One therapist stated:

When a patient was not able to login, the webmaster provided a link. The patient then neglected this link. If someone helps you, as a patient you must go for it and say "OK thank you, I will try again, and if it doesn't work, I will mail you again." [Female MBCT therapist, 62 years, 10 years of experience, no prior eMBCT experience]

Writing Fluency

Therapists indicated that a lack of writing skills made it difficult to understand patients' messages. One therapist stated:

Sometimes it was difficult to read past the spelling mistakes and to actually see what someone meant, and not to write down constantly "what do you mean?" [Female MBCT therapist, 58 years, 11 years of experience, prior eMBCT experience]

DISCUSSION

Principal Findings

The aim of this study was to gain qualitative understanding of the facilitators and barriers of eMBCT in a sample of heterogeneous cancer patients. Both eMBCT completers and dropouts participated in posttreatment interviews. Moreover, we conducted a focus group interview with eMBCT therapists. In all, this study adds to the existing quantitative evidence for eMBIs in cancer [7,8] by providing a qualitative perspective. Four overarching themes emerged, which were largely convergent between patients and therapists: treatment setting, treatment format, role of the therapist, and patient characteristics. Patients and therapists are much more flexible in when, where, and how they engage in eMBCT compared with group-based MBCT.

However, most eMBCT advantages seemed to come at a price. When patients and therapists mentioned a certain aspect as facilitating (eg, the individual setting: not having to cope with other patients' stories), they also mentioned it as barrier (no peer support).

Patients and therapists reported similar advantages and disadvantages of the timing, the individual nature, the asynchronous nature (for patients, this was detrimental to the relevance of therapist feedback, and for therapists, this was a threat to treatment continuity), the diaries, and the importance of self-discipline. The fact that so many aspects of the eMBCT were mentioned both as facilitator and barrier emphasizes the importance of offering flexibility in eMBIs.[21]

There were also differences between patients and therapists. As known from a previous qualitative study on eMBCT [21], bearing the responsibility for time management was a barrier for patients. For therapists, the eMBCT seemed to require a larger time investment compared with group-based MBCT. Moreover, therapists were more concerned with the (vulnerability of) continuity of the training. They also mentioned that missing out on nonverbal information rendered them unable to spot patient withdrawal at an early stage, and to determine the reason for empty diaries. Furthermore, therapists seemed more bothered by communicating mindfulness values in eMBCT than patients. Patients specifically mentioned asynchronicity as barrier to the role of the therapist because the asynchronous communication hindered emergence of a dialogue.

Clinical Implications

Although studies to date do not suggest that differences between how therapists handle the contact with their clients explain much variance in treatment outcome [16], the necessity of training and support for Internet-based therapists should be acknowledged. New eMBCT therapists should understand the importance of flexible availability and the dynamics of asynchronous interaction to pick up early signs of patient withdrawal.

The current eMBCT was individual, asynchronous, and therapist-assisted. One important adaptation may be to offer a peer support group.[26] The group context in MBIs supports perspective taking and the transition from personal story into investigation of common patterns of distress [6], and may foster skills relevant to valuing self and feeling close to others, which may help participants feel less isolated.[21] As a stand-alone intervention, formal online peer support group interventions for cancer patients have demonstrated preliminary feasibility and effectiveness.[27]

Another consideration may be to employ a synchronous videoconferencing format. [13] This takes away the barriers associated with asynchronous delivery and may facilitate dialogue with the therapist and peer support. A possible caveat may be that videoconferencing does not alleviate the scheduling issues inherent in group eMBIs [13] and that synchronous videoconferencing solutions are technically much more demanding. An alternative to videoconferencing may be to include synchronous written conversations (or "chats") with therapists or trained volunteers. Chats are becoming increasingly popular as Web-based mental health interventions by themselves and show inconclusive but promising evidence .[28]

Eventually, one could employ a blended format, combining the advantages of Web and group-based therapy.[29] Blended eMBIs could have group-based group meetings at

the start, midst, and end of the programme. The meeting at the start of the intervention could be used to address practical and technical matters, a midtreatment meeting to address common barriers experienced by patients during practice, and meeting at the end to say goodbye to each other and support patients to take responsibility for the continuation of their mindfulness practice in the future. In between group-based sessions, patients could be offered online sessions. In our view, these practical arrangements could greatly improve the acceptability and effectiveness of eMBCT.

Research Implications

Previous studies have provided encourageing quantitative evidence, for example, eMBIs in cancer patients.[13] Together with this study, these results provide support for a larger, quantitative trial directly comparing eMBCT with group-based MBCT for cancer patients. Moreover, it would be interesting to directly compare individual eMBCT with individual group-based MBCT. Future trials should test for differences in treatment accessibility, program adherence, and treatment outcome between eMBCT with and without peer support, with and without synchronous communication modalities, and with and without therapist assistance.[17] This would allow us to further elucidate the predictors and mediators of treatment effect in Internet-based interventions [30] to help us determine which patient to offer group-based versus Internet-based treatment. Moreover, all of the abovementioned design alterations likely impact cost-effectiveness of the interventions, which should be considered.[31] Thus, future studies should preferably assess how different eMBCT delivery formats influence program adherence, mindfulness skills, and treatment outcome, and how different versions of eMBCT delivery formats compare both qualitatively and quantitatively with group-based MBCT.

Strengths and Limitations

This is the first study to qualitatively explore facilitators and barriers of eMBCT for cancer patients. The relatively large sample size enabled us to reach data saturation and report a broad view of experiences. Moreover, we interviewed both completers and dropouts. Furthermore, we had the opportunity to gather data in the therapists. Nevertheless, our results should be interpreted within the limitations of our findings. We did not perform member checks to ensure validity of the verbatim transcripts. Moreover, the sample of the larger RCT consisted of cancer patients who self-selected themselves for a trial on an MBI. This implies that our findings cannot be extrapolated to cancer patients in general. In addition, some patients or therapists who participated in the training and were invited for focus groups or individual interviews declined participation, which may further limit the generalizability of our findings to all participating patients.

Conclusions

We aimed to gain understanding of the facilitators and barriers of individual, asynchronous, and therapist-assisted eMBCT for cancer patients. Patients and therapists reported similar advantages and disadvantages of the timing, the individual nature, the asynchronous nature, the diaries, and the importance of self-discipline. Future studies should assess how different eMBCT delivery formats could further improve treatment accessibility, program adherence, and treatment outcome.

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Chapter 6

Cost-effectiveness of individual Internet-based and face-to-face Mindfulness-Based Cognitive Therapy compared to Treatment As Usual in reducing psychological distress in cancer patients

Revised and resubmitted

ABSTRACT

Objective

It was previously determined that group-based face-to-face MBCT (MBCT) and individual internet-based MBCT (eMBCT) are equally efficacious compared to treatment as usual (TAU) in reducing psychological distress. In this study the incremental cost-effectiveness of both interventions compared to TAU was assessed.

Methods

This cost-effectiveness study included 245 self-referred heterogeneous cancer patients with psychological distress who were randomized to MBCT, eMBCT or TAU. Healthcare costs and (informal) work-related productivity losses were assessed by interview. Outcomes were expressed in EuroQol-5D-3L utility scores and Quality Adjusted Life Years (QALY). An economical evaluation with a time-horizon of 3 months was conducted from the societal perspective in the intention-to-treat sample. In addition, secondary explorative analyses of costs and quality of life during the 9 month-follow-up were conducted based on linear extrapolation of TAU.

Results

Paid work-related productivity losses and societal costs were lower in both intervention conditions compared to TAU during the 3-month intervention period. Moreover, quality of life (utility scores) improved in eMBCT versus TAU (Cohen's *d*: .54) and MBCT versus TAU (.53). At a willingness to pay of €20000 per QALY, the mean incremental net monetary benefit was €1916 (*SD*=€783) in eMBCT and €2365 (*SD*=€796) in MBCT versus TAU. Exploration of costs demonstrated an equal pattern of eMBCT and MBCT being superior to TAU. Quality of life at 9 months follow-up remained improved in both interventions.

Conclusions

Results indicate that eMBCT and MBCT are cost-saving treatments whilst simultaneously improving quality of life for distressed cancer patients.

BACKGROUND

Psychological distress is a negative emotional experience which impedes coping with cancer and its treatment.[1] Psychological distress is highly prevalent in cancer patients[2] and results in serious consequences such as reduced quality of life, decreased compliance with medical care, prolonged duration of hospital stay[3, 4] and increased (inadequate) healthcare use.[5] Although not all distressed cancer patients subsequently wish for psychological treatment[6], the availability of effective treatment for psychological distress in cancer patients is required.

Psychological treatment in cancer patients yield small to medium effects in reducing psychological distress.[7] In addition to cognitive behavioural therapy, Mindfulness-based interventions (MBIs)[8, 9] are offered in oncological settings. Several randomized controlled trials (RCTs) indicate that MBIs result in significant improvements of depressive and anxiety symptoms in cancer patients.[10-16]

MBIs are usually offered as an eight-week, face-to-face group training. However, attending group-based MBI is not always possible for cancer patients due to illness, anticancer treatments, fatigue and/or limited transportation options.[17] Internet-based interventions, on the other hand, are easily accessible, available 24/7 when delivered asynchronously and save travelling time.[18, 19] A recent multicentre RCT in 245 self-referred heterogeneous cancer patients with (mild) psychological distress showed that both group-based Mindfulness-based Cognitive Therapy (MBCT) and individual internet-based MBCT (eMBCT) had a significant and moderate effect in reducing psychological distress in comparison to Treatment as Usual (TAU).[15] The uncontrolled follow-up period of 9 months demonstrated consolidation of treatment effects in both interventions, with a slightly better effect in the eMBCT than MBCT condition.[20]

However, it remains unknown whether (e)MBCT provides value for money.[21] A study in 129 breast cancer patients suffering from persistent pain explored cost-effectiveness of MBCT compared to wait-list control with a time horizon of 6 months. When willingness-to-pay (WTP) was €0, the MBCT intervention was cost-effective with a probability of 85% and remained cost-effective with a probability of 70% to 82% when smaller effect and higher MBCT costs were assumed.[22] Another study in 104 breast cancer patients compared the cost-effectiveness of Mindfulness-Based Stress Reduction (MBSR) to wait-list controls with a time horizon of 12 weeks. MBSR was more costly ($+666) with an incremental QALY gain of +0.03 compared to wait-list controls, resulting in an ICER of $22,200/QALY.[23] Another study in 191 breast cancer patients investigated the cost-effectiveness of Mindfulness-Based Art Therapy (MBAT) compared to an active support

group with a time horizon of 9 weeks. MBAT demonstrated the potential to achieve parity with the support group intervention if some intervention-related costs were reduced.[24]

In short, the first studies demonstrate a tentatively positive view of the economic potential of MBIs. However, these studies included homogeneous samples of breast cancer patients and did not include an economic evaluation of an electronically delivered format of MBCT. Therefore, the primary aim of the current study was to evaluate the cost-effectiveness of both eMBCT and MBCT compared to TAU in a heterogeneous sample of distressed cancer patients from the societal perspective in the period from baseline (T0) to post-treatment (T1). The secondary aim was to explore costs and quality of life during the 9 month-follow-up (12-month time horizon) based on a linear extrapolation of TAU.

METHODS

Trial design, participants, procedure

Study methods have been described in detail elsewhere.[15] The present study is an economic evaluation from a societal perspective based on the results of a three-armed multicentre, parallel group randomized controlled trial comparing the effectiveness of eMBCT and MBCT to TAU in reducing psychological distress in cancer patients. Randomization was stratified for treatment centre and minimized for anticancer treatment intent (curative/palliative) and cancer type (breast/other). As patients randomized to TAU received either eMBCT or MBCT after the control period, the time horizon of the economic evaluation was restricted to 3 months.

Inclusion criteria were: a) any cancer diagnosis, any tumour type or stage, at any time in the past, on or off treatment; b) a score of ≥ 11 on the Hospital Anxiety and Depression Scale (HADS);c) ability to attend MBCT both face-to-face and online; and d) good command of the Dutch language. Exclusion criteria were: a) severe psychiatric morbidity such as suicidal ideation and/or current psychosis; b) change in psychotropic medication dosage within a period of three months prior to baseline; c) current or previous participation in ≥ 4 sessions of an MBI. Patients were recruited from April 2014 to December 2015 via self-referral. The study was approved by the ethical review board of the Radboud University Medical Center (CMO Arnhem-Nijmegen 2013/542) and all centers provided local ethics approval. The study was registered on Clinicaltrials.gov (NCT02138513), reported following CONSORT guidelines.[25] A protocol paper was published in advance.[26] All participants provided written informed consent prior to enrolment.

Interventions

Face-to-face MBCT

The MBCT protocol[9] was followed except for slight tailoring to the cancer patient. MBCT consisted of eight weekly 2.5h group sessions guided by a therapist, a six-hour one-day silent retreat and daily home practice assignments of about 45 minutes. All therapists in this study were accredited in concordance with the UK Mindfulness-Based Teacher Trainer Network Good Practice Guidelines.

eMBCT

The eMBCT was identical to MBCT in terms of content but was delivered individually and included weekly asynchronous written interaction with a therapist over email. For more information on this intervention we refer to our other work.[15, 19]

Treatment as usual

Treatment as usual (TAU) consisted of all healthcare patients wished to receive. There were no restrictions on healthcare utilization during the study period, except they were asked not to participate in MBIs.

Measures

Healthcare costs

The Trimbos/iMTA questionnaire for Costs associated with Psychiatric illness (TiC-P) [27] was used to collect information on direct healthcare use (e.g. general practitioner, mental healthcare and hospital day care visits) and paid and informal work-related productivity losses. The TiC-P is a self-report instrument, but in the current study the TiC-P was administered by the researchers in an interview format. The recommended time-horizon for determining healthcare costs by TiC-P of three months was used.[27]

Direct healthcare costs were calculated by multiplying volumes of care by standardized unit prices indexed using Dutch national price indices to the 2016 price level[28] (see Supplementary Table 1 (online only)). Prescription medication costs were retrieved from the Dutch national tariff list in 2017 (https://www.medicijnkosten.nl). Total, or societal, costs were calculated as the sum of medical and formal and informal productivity loss costs for T1, T1+T2, and T1+T2+(T3*2), reaching a time horizon of 12 months (9 months post-treatment).

Indirect costs – paid and informal work-related productivity losses

Indirect costs due to paid work-related productivity losses included *absenteeism* and *presenteeism* costs. *Absenteeism* costs - paid-work productivity losses due to absence

- were calculated by multiplying the number of hours patients were absent from their job by the gross wage per hour according to the Dutch guideline for health economic evaluations.[29]

Presenteeism costs – paid-work productivity losses due to being sick while at work - were calculated by multiplying estimated number of work hours lost by gross wage per hour. Indirect costs related to paid work-related productivity losses were calculated according to the Friction Cost (FC) method.[30] The friction period is the period needed to replace the ill worker and to restore the initial production level. A friction period of 85 days was used. When patients were ill for a period longer than 4 weeks and shorter than the friction period, a maximum of 21.7 sick days were counted in accordance with guidelines.[29] Once patients met the friction period criterium of >85 sick days at a specific time point (starting count at baseline) no additional indirect costs due to work were included during the rest of the study period.

Indirect costs related to productivity loss in informal work was measured by multiplying the estimated amount of hours others took over informal work the patient due to illness by the gross estimated costs per hour.[29] The recall period for paid and informal work-related productivity losses was 4 weeks (as per default). When applicable, both paid and informal work-related costs were proportionately extrapolated from 4 weeks to 3 months to match the recall period of the healthcare use questionnaire. Dutch national price indices were used to index healthcare and productivity costs to the 2016 price level[28] and costs were presented in Euros.

Intervention costs

Additionally, intervention costs were €299.00 per person for patients participating in the MBCT and €331.16 per person for patients participating in eMBCT (see Supplementary Table 2 (online only)). In MBCT, travel and parking related costs were calculated on an individual basis.[29] Intervention development costs were regarded as sunk costs and were therefore disregarded because they would not need to be repeated if the intervention were adopted on a broader scale.[31]

Quality of life

To measure the health-related quality of life (QoL) of cancer patients, a validated health-related QoL instrument was used: the EuroQol-5D-3L (EQ-5D).[32, 33] The EQ-5D index is obtained by applying predetermined weights to the five domains. This index gives a societal-based global utility score of the participant's health status on a scale with 0

(death) and 1 (perfect health). From the utility scores at T0 and T1 QALYs were calculated for each patient using the Area Under the Curve (AUC) method: ((EQ5D T0 + EQ5D T1) / 2) * (3/12).

Linear extrapolation

One way to deal with extrapolation of a cost pattern is to assume a linear relationship between costs and volume within some relevant range. Within that relevant range, the total cost varies linearly with volume, at least approximately. Outside of the relevant range, we presume the assumptions about linear cost behavior may be invalid. In terms of somatic care, patients followed clinical routine with which we did not intervene and which would remain similar after TAU. With regard to psychological care it is known that psychological distress levels are associated with healthcare consumption[5] and these did not change in patients receiving TAU only.[15] Therefore, the T1 measurement in TAU was linearly extrapolated up to 12 months.

Analyses

Descriptive analyses of mean differences between conditions were tested by one-way ANOVAs including treatment (eMBCT, MBCT or TAU) as independent variable and healthcare costs/ paid work costs / informal work costs / societal costs / EQ-5D utility scores / QALYs as dependent variable on the complete-case intention-to-treat (ITT) sample. Analyses of follow-up costs per category included costs at baseline as a covariate. Post-hoc tests were conducted by simple contrasts using TAU as reference group with Bonferroni-corrected (due to two comparisons to TAU) one-sided *p*-values (considering the positive clinical RCT) rendering $p \leq .05$ as significant. Cohen's *d* effect sizes (ES) were calculated by dividing the difference in means by baseline pooled *SD*s of the respective conditions[34] and in accordance with Cohen's guidelines, were interpreted as small (0.2 to 0.5), medium (0.5 to 0.8), or large (.8).[34] Cost-effectiveness analyses were conducted from the societal perspective on the complete-case ITT sample including all patients who filled-out the TiC-P and EQ-5D at T1, T2 and T3. The mean healthcare costs per person were compared across groups. The bootstrapped replications were graphed on two cost-effectiveness planes (eMBCT vs. TAU and MBCT vs. TAU). The horizontal axis of these planes represents the incremental effects and the vertical axis represents the incremental costs. The QALY model assumes WT*P*= willingness to accept compensation.

In addition, the net monetary benefit (NMB) was determined: NMB = (effect E of intervention expressed in QALY * WTP) – costs C for intervention. If the incremental NMB ($\Delta E * WTP - \Delta C$) is > 0, the intervention is considered to be cost-effective compared to an alternative. For the exact WTP is unknown, results of regression analyses with the

NMB as dependent variable were subsequently used to obtain a cost-effectiveness acceptability curve (CEAC) by plotting 1-*p*/2 against different levels of WTP (0, 20000, 40000, 60000, 80000) for a QALY where *p* is the p-value from the coefficient on the treatment dummy variable in the regression analyses.[35]

RESULTS

Sample characteristics

In total, 245 self-referred heterogeneous cancer patients with psychological distress were randomly assigned to eMBCT (*n*=90), MBCT (*n*=77) or TAU (*n*=78) (See Figure 1). The three conditions did not differ in terms of baseline demographic or clinical characteristics (see Table 1). Intervention dropout was significantly higher in the eMBCT than in the MBCT group: ($\chi^2(1, n=167) = 3.92$, $p = .047$). Study dropout (number of missing measurements at end of treatment) did not differ between conditions. However, patients who dropped out from the study demonstrated significantly higher psychological distress scores compared to those who completed measurements ($F(1,244)=5.82$, $p=.017$). There were no significant differences between conditions in direct healthcare utilization. The three conditions did not differ in employment status at baseline. Of the patients who had a job at baseline, relatively more patients met the friction period criterium in both interventions compared to TAU, although this difference was not significant ($\chi^2(2, n=245) = 5.25$, $p = .072$).

Cost-effectiveness: 3 month time-horizon

Costs

Direct healthcare costs did not significantly differ between the two intervention conditions and TAU (see Table 2). Costs associated with paid work-related productivity losses were lower in both eMBCT and MBCT compared to TAU ($p=.014$ and $p=.002$, respectively). Costs associated with informal work did not differ significantly between conditions. Societal costs were significantly lower in both eMBCT and MBCT compared to TAU ($p=.025$ and $p=.014$).

Quality of life

When QoL was expressed in EuroQol-5D-3L utility scores, patients in the eMBCT and MBCT conditions reported significantly higher QoL at T1 than patients in TAU ($F(2,198)=8.02$, $p < .001$, see Table 2) with moderate effect sizes (eMBCT vs. TAU = .54 and MBCT vs. TAU = .53) . When QoL was expressed in QALYs, there was a nonsignificant difference in favour of both interventions compared to TAU ($F(2,198)=2.80$, $p = .063$) with small to moderate effect sizes (eMBCT vs. TAU = .36 and MBCT vs. TAU = .34).

TABLE 1: Baseline Sociodemographic and Clinical Characteristics (*n*=245).

Characteristic	All *n*=245 n (%)	eMBCT *n*=90 n (%)	MBCT *n*=77 n (%)	TAU *n*=78 n (%)	
Sex					0.912
Female	210 (85.7)	77 (85.6)	67 (87.0)	66 (84.6)	
Male	35 (14.3)	13 (14.4)	10 (13.0)	12 (15.4)	
Age, years					0.464
Mean	51.7	52.4	52.1	50.4	
SD	10.7	10.7	11.4	9.9	
Married / in a relationship					0.491
Yes	202 (82.4)	76 (84.4)	65 (84.4)	61 (78.2)	
No	43 (17.6)	14 (15.6)	12 (15.6)	17 (21.8)	
Children					0.314
Yes	169 (69.0)	65 (72.2)	48 (62.3)	56 (71.8)	
No	76 (31.0)	25 (27.8)	29 (37.7)	22 (28.2)	
Education					0.451
High	166 (67.8)	56 (62.2)	54 (70.1)	56 (71.8)	
Middle	77 (31.4)	34 (37.8)	22 (28.6)	21(26.9)	
Low	2 (0.8)	0	1 (1.3)	1(1.3)	
Diagnosis					0.724
Breast cancer	151 (61.6)	53(58.9)	53 (68.8)	45 (57.7)	
Gynecological cancer	18 (7.3)	9 (10.0)	2 (2.6)	7 (9.0)	
Prostate cancer	16 (6.5)	7 (7.8)	6 (7.8)	3 (3.8)	
Colon cancer	12 (4.9)	4 (4.4)	4 (5.2)	4 (5.1)	
Non-hodgkin's lymphoma	11 (4.5)	3 (3.3)	1 (1.3)	7 (9.0)	
Skin cancer	5 (2.0)	3 (3.3)	1 (1.3)	1 (1.3)	
Thyroid cancer	4 (1.6)	1 (1.1)	1 (1.3)	2 (2.6)	
Bladder cancer	4 (1.6)	2 (2.2)	1 (1.3)	1(1.3)	
Neuroendocrine tumour	4 (1.6)	2 (2.2)	1 (1.3)	1 (1.3)	
Other	20 (8.2)	6 (6.7)	7 (9.1)	7 (9.0)	
Years since diagnosis					0.616
Mean	3.5	3.3	3.9	3.2	
SD	4.7	4	5.7	4.3	
Anticancer treatment intent					0.472
Curative	206 (84.1)	74 (82.2)	68 (88.3)	64 (82.1)	
Palliative	39 (15.9)	16 (17.8)	9 (11.7)	14 (17.9)	

TABLE 1: Continued.

Characteristic	All *n*=245 n (%)	eMBCT *n*=90 n (%)	MBCT *n*=77 n (%)	TAU *n*=78 n (%)	
Current treatment					0.694
None	133 (53.1)	49 (54.4)	43 (55.8)	41 (52.6)	
Hormone therapy	79 (32.2)	28 (31.1)	22 (28.6)	29 (37.2)	
Combination of treatments	12 (4.9)	4 (4.4)	4 (5.2)	4 (5.1)	
Immunotherapy	9 (3.7)	5 (5.6)	1 (1.3)	3 (3.8)	
Radiotherapy	8 (3.3)	3 (3.3)	5 (6.5)	0	
Chemotherapy	4 (1.6)	1 (1.1)	2 (2.6)	1 (1.3)	

Cost-effectiveness

The cost-effectiveness planes (Figure 2) revealed that the vast majority cost-effective pairs are located in the south-east quadrant where both interventions are more effective and less costly than TAU, i.e., dominate TAU. At a WTP of €20000 the mean incremental net monetary benefit was €1916 (*SD*=€783) in eMBCT versus TAU and €2365 (*SD*=€796) in MBCT versus TAU. The Cost-effectiveness Acceptibility Curve (CEAC) indicated that the probability of both interventions being cost-effective hovers around 99% regardless of the level of WTP per QALY gained (see Figure S1 (online only)).

Exploration of costs and quality of life during the 9 month-follow-up

Costs

Healthcare costs were significantly lower in eMBCT and MBCT compared to TAU in (p = .035 and p = .048, respectively). Paid work-related costs were significantly lower in both interventions compared to TAU (both p = <.001). Informal work-related costs were significantly lower in both interventions compared to TAU (p = .022 and p =.009). Societal costs were significantly lower in both interventions compared to TAU (both p = <.001).

Quality of life

Patients in both interventions maintained the increased QoL over the follow-up period with no significant differences between eMBCT and MBCT.

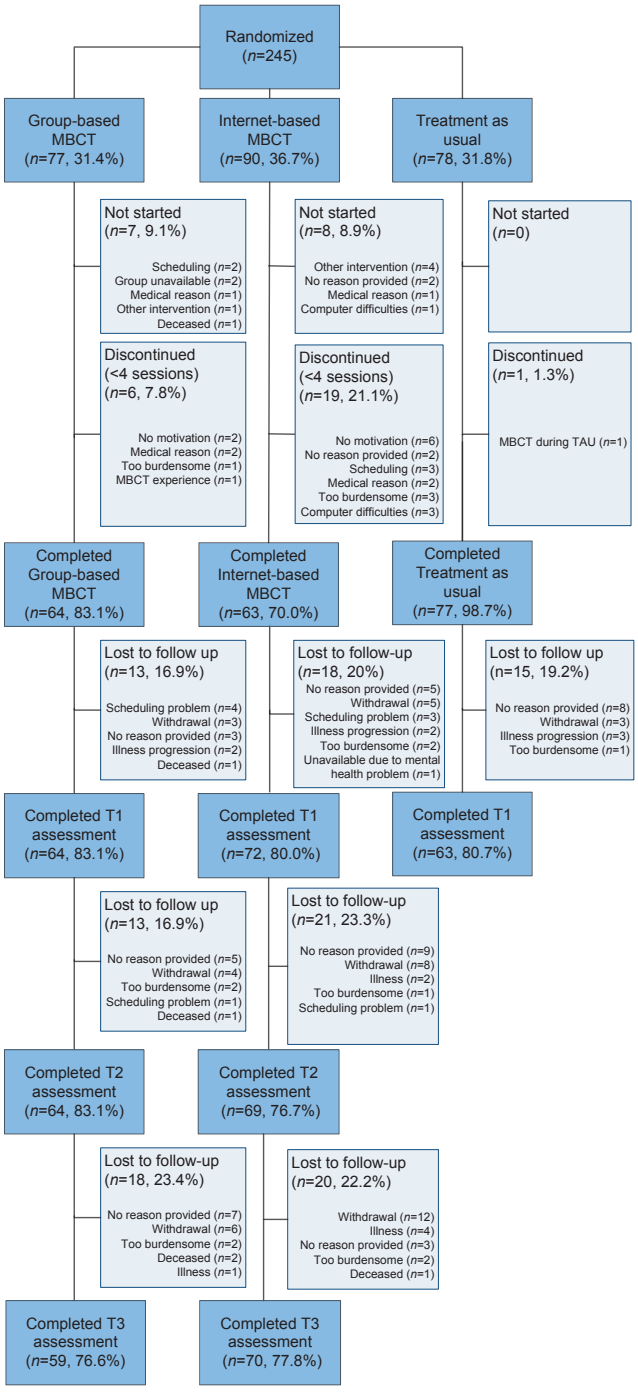

FIGURE 1: CONSORT flowchart of the cost-utility trial ran alongside clinical trial

TABLE 2: (Aggregated) costs per category in Euros and EQ-5D utility scores per condition and per measurement with TAU costs at T2 and T3 extrapolated from T1

	T0 Baseline				T1 End of treatment				T2 3-month follow-up				T3 9-month follow-up			
	eMBCT	MBCT	TAU	*p*	eMBCT	MBCT	TAU	*p*	eMBCT	MBCT	TAU	*p*	eMBCT	MBCT	TAU	*p*
n	90	77	78		72	64	63		63	59	63		59	53	63	
Healthcare																
M	1854.49	1858.76	1803.16	.99	1475.25	1090.34	1540.66	.28	2247.32	1739.45	3081.32	.05	3738.13	3869.22	6162.65	.08
SD	2289.15	2226.28	2244.21		1806.58	860.36	2437.17		2510.26	1276.21	4874.34		3650.48	4197.71	9748.67	
Paid work																
M	3148.11	3429.81	3782.71	.69	1287.42	1223.06	2698.39	.03	2467.57	1731.85	5396.78	.01	3519.78	2735.70	10793.57	<.001
SD	4814.55	4835.71	4548.91		3044.86	3011.54	3882.26		4509.08	3862.48	7764.52		7018.97	7229.30	15529.04	
Informal																
M	831.75	680.7	708.05	.57	490.18	408.43	663.53	.20	930.99	773.45	1327.06	.08	1492.88	1514.12	2654.12	.018
SD	1106.08	815.43	989.54		800.41	776.58	811.7		1352.01	1179.54	1623.41		1881.09	2258.14	3246.82	
Societal																
M	5834.35	5969.28	6293.91	.88	3252.85	2798.80	4902.58	.01	5645.88	4322.44	9805.17	<.001	8750.80	8199.31	19610.34	<.001
SD	6394.91	6149.18	5540.96		3888.31	3222.40	4895.04		5853.85	4063.20	9790.08		9056.53	9596.77	19580.16	
EQ-5D																
n	90	77	78	.92	72	64	63	<.001	69	64	63		70	59	63	
M	0.77	0.75	0.76		0.85	0.86	0.75		0.85	0.83			0.86	0.85		
SD	0.19	0.21	0.17		0.17	0.13	0.19		0.14	0.18			0.11	0.2		

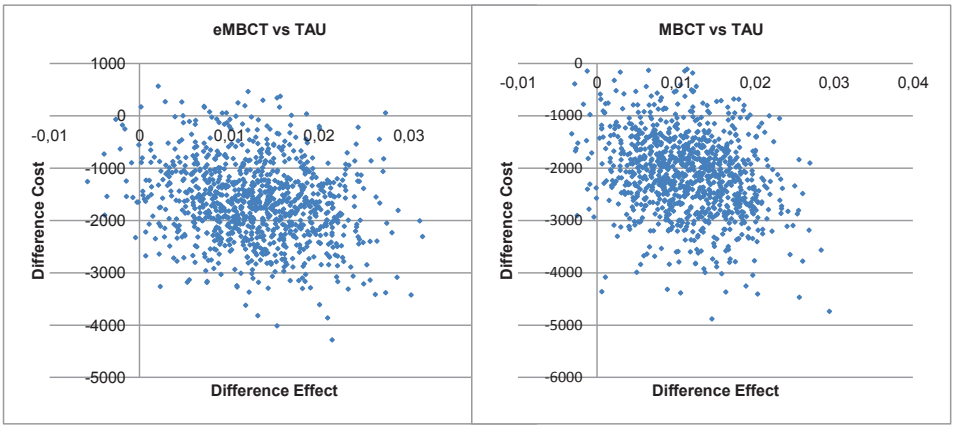

FIGURE 2: Incremental cost-effectiveness ratios (societal perspective) for both intervention conditions versus TAU during intervention period (T0-T1)

CONCLUSIONS

The aim of the current study was to evaluate the cost-effectiveness of both eMBCT and MBCT compared to TAU from the societal perspective in the period from baseline (T0) to post-treatment (T1) and to explore development of costs and quality of life during the 9 month-follow-up results in the period from baseline to 9 month-follow-up (T3) in a sample of self-referred (mildly) distressed cancer patients. Because the TAU condition did not have a follow-up beyond T1, possible long-term effects of both interventions compared to TAU were explored by linearly extrapolating the T1 measurement of TAU to T2 and T3.

Healthcare costs and informal work-related productivity losses did not significantly differ between conditions, costs associated with paid work were lower in the interventions compared to TAU. Importantly, the aggregated societal costs were significantly lower in both interventions compared to TAU at all post-treatment measurements – despite the added intervention costs. Patients in the eMBCT and MBCT conditions reported significantly higher QoL at T1 than patients in TAU with moderate effect sizes, although there were no significant differences between conditions in terms of QALYs. This latter might be explained as a power issue, as the difference demonstrated a nonsignificant trend in favour of both interventions compared to TAU.

Several psychosocial interventions have previously been demonstrated to represent good value for money in cancer care.[36] A review of 11 cost-effectiveness studies of psychosocial interventions in cancer care indicate cost-effectiveness at different WTP thresholds, but that more research is necessary and that more research should be performed encompassing potential important cost drivers from a societal perspective, such as productivity losses or informal care costs.[37]

The current results are partly in line with previous findings on cost-effectiveness of MBIs for cancer patients [22-24] although it must be noted that there are considerable differences between the studies in terms of population, format of the MBI, from which perspective the cost-effectiveness analysis was conducted and whether authors used a disease specific or generic QoL measure. Moreover, the current results indicate cost-savings. Most likely, this discrepancy with the most comparable study to date[23] is the result of the self-referred nature of the current sample as previous research indicates that higher levels of mental comorbidity results in higher healthcare costs in cancer patients.[5]

Study limitations

The most important limitation is lack of follow-up for the TAU group, which rendered it impossible to empirically determine long-term cost-effectiveness of both interventions compared to TAU. However, extrapolated follow-up results demonstrated comparable favourable effects of both interventions compared to TAU. Moreover, number of dropouts were significantly higher in the eMBCT than in the MBCT group. Lower usage than intended is a known problem in e-health intervention research[38] although it should be mentioned that not using the technology as defined or implied by its creators is not equal to non-adherence or to the participant is not using the technology at all. Patients could also drop-out because they experience sufficient improvement in psychological distress.[39]

Clinical implications

These results imply that offering Internet-based MBCT in clinical practice improves accessibility of psycho-oncological care whilst saving societal costs, without compromising intervention efficacy.

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Chapter 7

Summary and general discussion

SUMMARY

The present thesis focused on examining the effectiveness and cost-effectiveness of group-based Mindfulness-based Cognitive Therapy (MBCT) and Internet-based MBCT (eMBCT) compared to Treatment as Usual (TAU) in a sample of 245 distressed cancer patients.

The introductory chapter highlighted the background and relevance of this thesis. It described how many patients suffer from psychological distress, what the consequences of psychological distress in cancer patients are, what evidence-based psychological treatments for distressed cancer patients entail and what problems exist in the context of accessibility of evidence-based psychological treatments of cancer patients.

Chapter 2 explored the hypothesis that presence of psychiatric disorder and psychological distress is associated with increased healthcare utilization and costs. The study population consisted of the 245 mixed-cancer patients with at least mild symptoms of psychological distress (Hospital Anxiety and Depression Scale–T ≥ 11) who participated in the larger Randomized Controlled Trial (RCT). Patients were assessed with Structured Clinical Interview for DSM-IV-TR Axis I Disorders (SCID-I) for depressive, anxiety, and/or adjustment disorder. Psychological distress was measured by the HADS. Retrospective self-reported healthcare utilization in the past 3 months was collected by means of the TiC-P, a self-report questionnaire which was assessed in an interview-format together with one of the researchers. Associations between psychiatric disorder, psychological distress and healthcare utilization were assessed in terms of incidence rate ratios and costs per category (mental, primary, somatic, and complementary) were assessed by negative binomial, logistic, and gamma regression. In total, 36% of patients suffered from psychiatric disorder, which was associated with mental healthcare utilization and costs. We observed a trend of higher somatic healthcare utilization in patients with psychiatric disorder. Psychological distress appeared to be associated with higher mental healthcare utilization and costs. Furthermore, psychological distress was also associated with complementary healthcare utilization.

The BeMind study, as described in Chapter 3 and 4, concerned a three-armed multicenter RCT in 245 mixed-cancer patients who were randomly allocated to MBCT (*n*=77), eMBCT (*n*=90) or TAU (*n*=78) and who suffered from at least mild psychological distress (Hospital Anxiety and Depression Scale (HADS) ≥ 11). Primary outcome was post-treatment psychological distress (HADS). Linear mixed-modelling was conducted in the intention-to-treat sample on the continuous outcomes. Dropout from the interventions was significantly higher in the eMBCT than in the MBCT group. Patients

reported significantly less psychological distress in both MBCT interventions compared to TAU. In addition, post-treatment prevalence of psychiatric diagnosis was lower in both MBCT (33% improvement) and eMBCT (29%) in comparison with TAU (16%), but these changes were not significant. Both interventions reduced fear of cancer recurrence, rumination and increased mental health-related quality of life, mindfulness skills and positive mental health compared to TAU. Physical health-related quality of life did not improve.

Chapter 5 aimed to explore facilitators and barriers of individual asynchronous therapist-assisted eMBCT as experienced by both patients and therapists. In total, 31 patients participated in an individual post-treatment interview and eight therapists were interviewed in a focus group interview. Four overarching themes emerged which were largely convergent between patients and therapists: treatment setting, treatment format, role of the therapist, and patient characteristics. With regard to treatment setting, both patients and therapists mentioned that they are much more flexible in when, where, and how they engage in eMBCT compared with group-based MBCT. Both patients and therapists reported that they were facilitated by this sense of autonomy in the eMBCT. Patients indicated that they did not have to cope with other patients' stories. Therapists indicated that they were better able to tailor the intervention to individual themes.

There were also differences between patients and therapists. For therapists, the eMBCT seemed to require a larger time investment compared with group-based MBCT. With regard to treatment format, patients specifically mentioned asynchronicity as barrier to the role of the therapist because the asynchronous communication hindered emergence of a dialogue. Therapists were more concerned with the (vulnerability of) continuity of the training. They mentioned that missing out on nonverbal information rendered them unable to spot patient withdrawal at an early stage, and to determine the reason for empty diaries. Furthermore, with regard to role of the therapist, therapists sometimes experienced barriers in communicating mindfulness values in eMBCT, whereas patients felt they received the information on mindfulness values they needed.

Chapter 6 focused on the cost-effectiveness of both MBCT interventions compared to TAU. This cost-effectiveness study was conducted alongside the previously described RCT. Healthcare costs and (informal) work-related productivity losses were assessed by interview. Outcomes were expressed in EuroQol-5D-3L utility scores and Quality Adjusted Life Years (QALY). An economic evaluation with a time-horizon of 3 months was conducted from a societal perspective in the intention-to-treat sample. In addition, secondary explorative analyses of costs and quality of life during the nine month-

follow-up were conducted based on a linear extrapolation of TAU. Paid work-related productivity losses and societal costs were lower in both experimental conditions compared to the control condition TAU during the 3-month intervention period. Moreover, quality of life (utility scores) improved in eMBCT and MBCT versus TAU with moderate effect sizes. Results indicate that both eMBCT and MBCT are cost-saving treatments whilst simultaneously improving quality of life for distressed cancer patients. Exploration of costs demonstrated an equal pattern of eMBCT and MBCT being superior to TAU. Quality of life improvements at 9 months follow-up remained steady in both experimental interventions compared to the outcome at three months.

GENERAL DISCUSSION

The research in this thesis robustly illustrates that MBCT and eMBCT are effective alternatives to usual care, leading to less psychological distress, less fear of cancer recurrence, less rumination and more positive mental health and well-being and quality of life. Moreover, our cost-effectiveness study demonstrated dominance of both interventions compared to TAU, indicating lower societal costs and higher quality of life.

Our results in Chapter 2 explored the probability of the cost-offset effect, or the hypothesis that cancer patients use less of other (perhaps inadequate) healthcare services when psychological distress is reduced.[1] Psychiatric disorder was not related to healthcare other than mental healthcare. This contradicts previous findings indicating an association between psychiatric disorders and somatic healthcare use [2], although we did find a nonsignificant trend in this direction. In The Netherlands, the general practitioner might serve as gatekeeper referring distressed patients to mental rather than somatic healthcare. In line, tentative results indicated an association between depressive symptoms and primary healthcare visits. In contrast to psychiatric disorder, psychological distress of cancer patients was found to be significantly associated with healthcare use other than mental healthcare – complementary healthcare. In part, this discrepancy between psychological distress and psychiatric disorder might be caused by the fact that psychological distress as a continuous outcome measure carries more information compared to the dichotomous nature of psychiatric disorder as outcome measure. With regard to the association between psychological distress and complementary healthcare use, it is known that mainly anxiety symptoms are associated with use of complementary healthcare in cancer care [3, 4] and some have argued that this demarcates a lack of integration of psycho-oncological services.[5] Although a recent critical appraisal indicates that MBIs in cancer care recently reflect decreases in

sub-clinical symptomatology rather than relief of psychiatric disorders[6], results in this chapter indicate that even a decrease in sub-clinical symptomatology could perhaps prevent unnecessary and possibly inadequate healthcare utilization.

The results of the RCT (Chapter 3 and Chapter 4) are in line with meta-analyses of previous RCTs on MBIs for reducing psychological distress in cancer patients.[7, 8] These effects of most of these interventions were found to be sustained in the medium term and even long term.[9] In line with this, the follow-up study of the BeMind project (not included in the current thesis) also demonstrated consolidation of treatment outcome during the nine-month follow-up period. Interestingly, results even demonstrate further improvements in cancer patients' over time especially in eMBCT.[10]

Moreover, these results convincingly demonstrate that Internet-based MBCT renders MBCT much more accessible for cancer patients without extra costs and without compromising intervention efficacy. As many cancer patients experience barriers to participation in face-to-face psychological interventions.[11, 12], Internet-based delivery of psychological interventions might be especially powerful in the oncological context, where some many patients are hampered either by physical (e.g. travel distance) or mental barriers (e.g. not wanting to visit the hospital again).[13] Unfortunately, solid evidence for Internet-based MBIs in cancer care is virtually absent and the field is in dire need of well-conducted RCTs. One single controlled study (n=62) demonstrated feasibility of adapted internet-based MBSR for cancer patients.[14] Another pilot study confirmed that MBSR delivered via an iPad may be feasible and acceptable for breast cancer patients.[15] A recent RCT compared the effectiveness of a physiotherapy-led ambulant physical activity feedback (AAF) intervention to an individual internet-based MBCT intervention and psycho-education in n=167 cancer survivors. It was concluded that both interventions are effective for manageing fatigue severity compared to receiving psycho-educational emails.[16] The current study greatly contributes to the scarcely available evidence for Internet-based MBIs in cancer care.

Nevertheless, our qualitative research in Chapter 5 did indicate that there is much to be improved in the design and delivery of the Internet-based format. First, patients mentioned lack of peer support and the asynchronous communication with their therapist as disadvantages of Internet-based MBCT. Second, our RCT also demonstrated that the proportion of patients receiving a lower dosage of MBCT than intended was higher in Internet-based MBCT than in group-based MBCT. Patients dropped out due to lack of motivation, engaging in another intervention of preference and technical difficulties. However, the proportion of patients receiving a lower dosage of MBCT than intended was higher in internet-based MBCT, which although cost-effective

still was pretty resource intensive. Lower usage than intended is a known problem in e-health intervention research[17], although it should be mentioned that not using the technology as defined or implied by its creators is not equal to non-adherence or to the participant is not using the technology at all. Patients could also drop-out because they experience sufficient improvement in psychological distress.[18, 19]

Patients mentioned lack of peer support and the asynchronous communication with their therapist as disadvantages of internet-based MBCT. So, internet-based MBCT could and should be further improved to ensure adherence and scalability. Previous research indicated that increased interaction with a counsellor, more frequent intended usage, more frequent updates and more extensive employment of dialogue support significantly predicted better adherence.[17] This implies that technical improvement is necessary and possibly alternative modes of treatment delivery should be explored in future research.

The results of our cost-effectiveness analysis in Chapter 6 indicate that both MBCT and eMBCT have the potential to reduce societal costs already during the intervention period. This is a great achievement, as cost-effectiveness evaluations of psychological treatments are much needed in the field of psychosocial oncology [20] and in MBIs in general [21] to determine whether providing MBCT to cancer patients indeed is economically attractive. The current healthcare system increasingly asks for these studies as choices have to be made regarding optimal resource allocation. In this cost-effectiveness study, we not only included healthcare costs, but also gathered data on productivity losses, informal healthcare costs and used QALYs as an outcome measure. [20] The current results are partly in line with previous findings on cost-effectiveness of MBIs for cancer patients[22-24] although there is considerable heterogeneity in what circumstances previous cost-effectiveness analyses were conducted. For example, previous research on cost-effectiveness of MBIs is restricted to breast cancer patients. Moreover, we found MBCT to be cost-saving. This discrepancy with the most comparable study to date (Lengacher et al.[22]) is most probably the result of the self-referred nature of the current sample.

In short, our study on MBCT in cancer patients is the first to indicate that MBCT, both group- and Internet-based, yields lower psychological distress and higher quality of life whilst simultaneously saving societal costs.

Strengths

This thesis included the first large-scale RCT of eMBCT and MBCT in cancer patients in The Netherlands using a large, clinically representative heterogeneous sample of mixed-

cancer patients in different stages of disease. This is a strength, as breast cancer patients are overrepresented in studies on MBIs in cancer patients so far [6] and expansion of the evidence-base of psycho-oncological interventions in e.g. advanced, non-breast cancer in psycho-oncological research is necessary.[25]

Moreover, we employed a patient-centred self-selected recruitment method. In the BeMind study, we managed to accrue over 500 and to include 245 patients in a period of about 20 months. In previous psycho-oncological research, consecutive sampling of patients in hospital outpatient settings lead to recruitment difficulties.[26] Since psycho-oncology interventions differ from many other cancer treatments in that not all cancer patients would like treatment despite having psychological symptoms, self-referral recruitment can be less resource intensive than clinic-based consecutive recruitment and may facilitate more rapid attainment of recruitment targets.[27]

Furthermore, this study was conducted in a variety of clinical settings, again of benefit to the clinical representativeness.

With regard to choice of outcome measures, it may be of specific interest to the individual patient that MBCT does not only impact regulation and normalization of negative emotional experiences, but also at rediscovering aspects positive emotional well-being [28] which may, albeit overshadowed, still be present in the face of cancer. Becoming aware again of aspects of positive well-being may perhaps foster an upward spiral that might be promoted by MBCT.[29]

Concerning intervention fidelity, another strength is the use of protocolised MBCT. A recent systematic review indicated that MBIs in psycho-oncology are often poorly defined. [6] The MBCT curriculum used in both group and Internet-based MBCT interventions is primarily based on the MBCT program by Segal, Williams and Teasdale. [30] The program was slightly adapted to the oncology patient in terms of psycho-education and movement exercises. In both conditions, participants received guided mindfulness meditation exercises for home practice and a reader with home practice instructions and background information. The Internet-based MBCT intervention was similar to group MBCT in terms of protocollized curriculum content.

We took care of the quality of the MBCT intervention. Our mindfulness therapists, or teachers, fulfilled the advanced criteria of the Association of Mindfulness-based Teachers in The Netherlands and Flanders) which are in concordance with the UK Mindfulness-Based Teacher Trainer Network Good Practice Guidelines for teaching mindfulness-based courses.[31] In addition, all involved teachers had previous experience with providing

psychological care to cancer patients. Three full-day plenary supervision meetings were held during the intervention phase of the trial. All teachers are involved in both group and Internet-based MBCT. Teachers without prior Internet-based MBCT experience were provided with guidelines and supervised by more experienced Internet-based MBCT teachers. Group sessions were videotaped to evaluate teacher competence and protocol adherence using the Mindfulness-Based Interventions - Teachers Assessment Criteria (MBI-TAC)[32] by two independent therapists who evaluated two random sessions from each of the nine therapists providing face-to-face MBCT (who treated 80.8% of all patients receiving either intervention). Of the nine therapists rated, four were considered proficient, three competent and two beginner.

Limitations

In addition to the strengths of the current thesis, some limitations should be mentioned as well. Next to our primary research questions concerned at determining the efficacy of both MBCT interventions compared to TAU in reducing psychological distress at end of treatment, secondary research questions were also concerned with determining the consolidation of treatment effects over the course of the 9-month follow-up period. Due to ethical constraints, we chose to offer patients randomized to the TAU condition participation in one of the two interventions after three months. This did not allow us to determine whether consolidation of treatment effects is due to the MBCT interventions or simply due to natural recovery or regression to the mean, although it must be noted that we did not observe this tendency in the TAU group during the three month waiting-list period. Moreover, a dedicated power analysis for determining long-term effects, was omitted.

In addition to determining the long-term effects in the three-armed comparison, the RCT was not powered to directly compare or determine non-inferiority of eMBCT to MBCT, or in other terms to determine whether the new intervention (eMBCT) is not unacceptably worse than an intervention already in use (MBCT).

MBCT and eMBCT differed not only in intervention delivery (online versus face-to-face), but also in whether patient participated in a group setting together with peers or individually. Although a systematic review examining 43 studies on peer support programs for cancer patients demonstrated mixed results regarding its effectiveness on psychological well-being[33], participants often experience the peer group setting in MBIs as facilitating.[34] Qualitative research showed that the peer group setting in a MBSR setting for breast cancer patients provided an atmosphere which was experienced

as safe and supportive, which in turn stimulated mutual connections with and trust between fellow breast cancer patients.[35] This implies that the effects of intervention delivery and peer group support cannot be disentangled in the current study.

Our RCT did not include an active but a TAU control condition. The majority of mindfulness trials conducted with cancer populations have used wait-list control groups rather than active control or competing interventions.[36] Although this research design is reasonable during early intervention development and preliminary evaluation of efficacy, future studies on Internet-based MBCT need more rigorous designs, involving active control conditions.[21, 36] As a consequence, this study does not allow us to conclude whether MBCT and eMBCT are more effective than other evidence-based approaches for psychological and behavioural symptoms in patients with cancer, such as CBT. Nevertheless, TAU was clearly measured in the current study, which is an important improvement.[21] In The Netherlands, TAU can be considered to be of a high quality. In line, 31% of the included participants in the RCT received some sort of mental healthcare in addition to (e)MBCT as usual treatment during the intervention.

Future developments in treatment and research

MBIs have been investigated in an increasing number of studies and clinical applications in the past two decades. Dimidjian and Segal [21] painted a broader picture of the status quo on the evidence base for MBIs within a framework of clinical psychological science using the National Institutes of Health (NIH) stage model.[37] This stage model describes different phases of intervention research, starting at stage 0 (basic, fundamental research) to stage V (implementation and dissemination). They argued that stage I (intervention development/refinement) and II (efficacy in research clinic). Many studies have investigated MBIs for an increasing variety of symptoms and populations using weak study designs and without proceeding to implementation. Stage III research is especially relevant for testing future improvements of MBI using web-based or other technology-based delivery tools without therapist guidance.[38] It is concluded that underpowered pilot trials (stage I and II are highly overrepresented. Future studies should focus on more on cost-effectiveness studies, and dissemination and implementation strategies.

With regard to Internet-based delivery of MBCT, the current thesis has generated food for thought. Internet-based MBCT has not yet met its full potential in its current format and needs to be improved to ensure patient-friendliness, accessibility and adherence. Poor intervention adherence is a common issue in Internet-based interventions that needs to be addressed.[17] Moreover, the Internet-based MBCT was resource intensive. This implies that adapted formats of Internet-based MBCT should be explored to

improve the adherence and scalability of the interventions. In line, we urge relevant parties such as healthcare insurance companies to provide financial support for the continuous development of e-health interventions beyond their initial conception.

As a possible solution, we envision two adapted Internet-based MBCT formats. First, as many patients mentioned disadvantages of online-only delivery in Internet-based MBCT, it seems useful to combine face-to-face group-MBCT sessions with additional Internet-based MBCT sessions in blended-MBCT. Blended-care interventions combine the advantages of face-to-face and Internet-based elements.[39] Second, as many cancer patients prefer self-help[11, 26] and unguided self-help interventions have previously demonstrated effectiveness for low-distressed cancer patients[40] the possibilities of unguided MBCT interventions should be explored. These interventions are extremely scalable with minimal costs. Although many unguided interventions show diminished user engagement, we know that technology itself can influence adherence and engagement to online interventions. Examples are the use of reminders that can help people to keep using an intervention[41] and gamification, i.e. the use of game design elements in non-game context, which has been shown to positive influence engagement.[42] Research has shown that an unguided intervention which leverages some of these technological features can be similarly effective as a guided online intervention.[43] Together, these interventions comprise the development of a mindfulness-based stepped-care programme with different levels of MBCT intensity corresponding with different patient needs and preferences.

Furthermore, we also need more research on long-term follow-up results. Long-term follow-up comparisons are often lacking in research on Internet-based interventions, impeding reliable long-term estimates.[13] Our follow-up study focused on the consolidation of the effectiveness of MBCT and eMBCT during the nine-month follow-up period. Findings suggested most improvements in cancer patients' increase over time after both interventions. Interestingly, patients seemed to benefit more from therapist-assisted Internet-based MBCT than MBCT based on psychological distress levels. Future RCTs should preferably include a longer comparison control group to determine long-term cost-effectiveness results.

To be able to predict what treatment (Internet-based or group-based MBCT) works best for whom, future research also needs to tap into predictors and moderators.[44] In our follow-up study, psychological distress, rumination and neuroticism and more extraversion and agreeableness at baseline predicted a better outcome at the nine-month follow-up after both interventions. Notably, less mindful and less conscientious patients at baseline benefited more from therapist-assisted Internet-based MBCT than

from MBCT. The individual therapist attention in Internet-based MBCT perhaps is of support to those patients who are less mindful and less conscientious. Furthermore, while patients in MBCT can refrain from discussing (the lack of) home practice by letting others in the group share their experiences, patients in eMBCT are more acknowledged for their home practice as they receive weekly written feedback from their therapist. Thus, eMBCT might encourage the less conscientious and mindful patients to complete their homework.[10] Future studies should put these tentative predictors and moderators to test.

Moreover, in order to understand the processes which account for therapeutic change[45, 46] , we should look into mediating variables, or intervening variables that tap into processes of change and which may serve a guide that points to possible mechanisms. A systematic review and meta-analysis of mediation studies in MBIs in various settings identified strong, consistent evidence for cognitive and emotional reactivity, moderate and consistent evidence for mindfulness, rumination, and worry, and preliminary but insufficient evidence for self-compassion and psychological flexibility as mechanisms underlying MBIs.[47]

With regard to comparing working mechanisms in group- and Internet-based MBCT, the concept of therapeutic alliance might be an important factor. Therapeutic alliance, or the achievement of collaborative, "work together" aspects of the of the therapeutic relationship between patient and therapist has shown to have a robust, albeit modest relation with treatment outcome across a broad spectrum of psychological treatments and client/problem contexts.[48] Research on the therapeutic alliance in Internet interventions exists but is still limited. A systematic review on the therapeutic alliance in Internet-based interventions indicated Internet-based interventions to be equivalent to face-to-face therapy in the development of therapeutic alliance. However, only a few studies have investigated this relationship.[49] It would be interesting in future trials in MBIs to examine if therapeutic alliance mediates the reduction of psychological distress or the increase of positive mental well-being after eMBCT compared to MBCT.

Although MBCT for distressed cancer patients is effective and saves money for distressed cancer patients, the reimbursement of MBCT in The Netherlands remains problematic. The Dutch National Health Insurance (Zorginstituut Nederland) advised the ministry to only reimburse MBCT for patients with psychiatric disorder. As only a minority of distressed cancer patients fulfil the diagnostic criteria for a psychiatric disorder, they cannot be offered MBCT. This implicates that an evidence based effective and cost-effective treatment is not publicly accessible for this population and therefore creates inequality in access between those patients able to afford the treatment and those that

cannot afford it. Nevertheless, it must be noted that MBCT is provided for all cancer patients at several locations throughout The Netherlands, e.g. at the own Radboud University Medical Centre and at several psycho-oncological institutes such as the Helen Dowling Institute. Moreover, the Helen Dowling Institute provides nationwide and health-care reimbursed online cognitive behavioural therapy for cancer patients inspired by the current eMBCT.

Nevertheless, we should direct efforts to implementation of MBIs in daily clinical oncological care for all patients who wish to receive MBCT. As Greer mentioned in 1994: "*The most immediately important task of psycho-oncology is to close the yawning gap between current knowledge and actual clinical care of patients"*.[50] This is easier said than done, as Rebecca Crane and Willem Kuyken, leading researchers in the field of MBIs eloquently illustrate [51]: *"Even if a psychosocial intervention has compelling aims, has been shown to work, has a clear theory-driven mechanism of action, is cost-effective and is recommended by a government advisory body, its value is determined by how widely available it is in the health service."*

In order to improve availability of MBIs in the UK health service, Crane and Kuyken have formulated recommendations for successful implementation of MBIs.[42] Their recommendations are based on extensive review of the evidence of what contributes to the likelihood of evidenced-based practice flourishing. These recommendations include:

- *Tailor and translate research findings to the local setting*: base decisions on providing MBCT on both research evidence and local service priorities
- *Engage in ownership of research or implementation process:* to positively affect uptake, engage key stakeholders and develop local networks; refrain from top-down forced research use in an organisation
- *Use "champion" enthusiasts*: e.g. former participants who are enthusiastic about the practice to promote new ideas, both within and outside a specific organisation
- *Analyse the implementation context*: we will need to explore factors that impede or facilitate implementation among local stakeholders by setting up an implementation steering group to ensure a tailored and systematic approach of local barriers and facilitators of implementation.
- *Ensure credibility of the evidence*: use of scientific results in clinical practice is enhanced by credible evidence, credible "champions" and a commitment to routine reporting of data to key stakeholders
- *Provide leadership*: Strong and facilitative leaders at project and organisational level can lend strategic support and authority to the process

- *Provide resources:* Implementation needs adequate resources and support including financial, human (dedicated project leaders) and appropriate equipment.

This implementation framework with its recommendations may strongly facilitate the transfer of MBCT knowledge into action in the daily practice of oncological care.

Moreover, implementation of MBIs in clinical practice means that the therapist pool should be enlarged and more MBI therapists need be trained. But what does it mean to be a good Internet-based mindfulness-trainer? Clinician training is an important challenge in MBIs, especially since MBI therapists are required to have a personal practice in mindfulness in addition to professional training in the clinical approach. There is a paucity of knowledge on clinical training in Internet-based interventions in general. There are some examples of studies focusing on the training of therapists in online CBT, e.g.[52] In this training, online CBT skills were emphasized, such as writing motivational feedback messages. The training consisted of 1.5 days and covers the implementation domains "knowledge", "skills", "motivation", and "organization", by focusing on the therapy's rationale, iCBT skills, and implementation strategies. Using an evaluation questionnaire, implementation determinants (therapist characteristics, e-health attitude, and implementation domains) and interventions acceptance were assessed among participants after training. The authors conclude that therapists' positive training evaluations were promising regarding the dissemination of online CBT in daily practice, but that as well as training therapists, creating an open atmosphere among managers and colleagues is important to ensure that the new intervention becomes part of the regular treatment options. However, there is no standard available for determining instructor quality in Internet-based MBIs [38] and similar clinical training methods in improving online MBI teacher competency should be developed.

EPILOGUE

More than ten years ago, the Helen Dowling Institute, as the oldest mental healthcare institute for cancer patients in The Netherlands, commenced to provide individual Internet-based MBCT (eMBCT) for cancer patients in clinical practice. This thesis was built upon this pioneering work.

The Dutch Cancer Foundation (KWF) has demonstrated willingness to cooperate in our mission to disseminate MBCT and Internet-based MBCT for cancer patients in clinical practice. Based on the results of this thesis, we conducted a budget-impact analysis together with KWF. The results of this budget-impact analysis were very positive, and the report was presented to the Secretary-General of the Dutch Ministry of Health in the Summer of 2018. With heartfelt dedication we trust that these efforts will contribute to future reimbursement of accessible and effective (Internet-based) psychological treatment for distressed cancer patients.

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Chapter 8

Appendix

Nederlandstalige samenvatting
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Donders Graduate School for cognitive neuroscience

NEDERLANDSTALIGE SAMENVATTING

Het aantal mensen dat moet leven met de gevolgen van kanker groeit

De incidentie en mortaliteit van kanker stijgt in rap tempo door veroudering en bevolkingsgroei. Dit fenomeen wordt ook wel *double ageing* genoemd. Mensen leven langer en het relatieve aandeel van mensen van 65 jaar en ouder neemt toe.[1] Ook worden er veranderingen verwacht in de prevalentie en de verdeling van de belangrijkste risicofactoren voor kanker.[2] De voorspelling is dat de incidentie van kankerpatiënten wereldwijd toeneemt van 12.7 miljoen gevallen in 2008 tot 22.2 miljoen in 2030.[3]

Mensen met kanker hebben vaak psychische klachten

Het is van groot belang dat patiënten met kanker worden gescreend op psychische klachten en psychisch welzijn.[4] Psychische klachten worden in het Engels vaak beschreven met het begrip *psychological distress.* Dit begrip wordt door het National Comprehensive Cancer Network (NCCN) gedefinieerd als "*een multi-factoriële onaangename emotionele ervaring van een psychologische (dat wil zeggen cognitieve, gedragsmatige, emotionele), sociale en / of spirituele aard die het vermogen om effectief om te gaan met de ziekte kanker en de fysieke symptomen en de behandeling ervan, beperken. De mate waarin er psychische klachten zijn, varieert van het hebben van normale gevoelens van kwetsbaarheid, verdriet en angsten tot problemen die invaliditeit kunnen veroorzaken, zoals depressie, angst, paniek, sociaal isolement en existentiële en spirituele crisis.*" Het begrip *psychological distress* kan daarmee worden geconceptualiseerd als een dimensionele uitkomstmaat in termen van hoeveelheid psychische klachten of als een dichotome uitkomstmaat in termen van aan- of afwezigheid van een psychiatrische stoornis. In totaal hebben tussen één op drie [5] en één op twee patiënten met kanker [6] last van klinisch significante psychische klachten.

De screening op psychische klachten kan worden gebruikt als een behoeftebepaling en als een bron van informatie om te bepalen of verwijzing naar psychologische of psychiatrische zorg noodzakelijk is.[4] Enkel screenen is echter niet genoeg: informatie over de ernst van de klachten moet worden aangevuld met contextuele informatie om de klachten te kunnen duiden.[7] Een positieve screening op psychische klachten is enkel een indicatie dat verdere beoordeling van individuele behoeften en, eventueel, passende verwijzing en behandeling nodig is.[8] Niet alle patiënten met kanker en psychische klachten wensen psychologische behandeling: sommige patiënten hebben bijvoorbeeld voldoende steun van familie en vrienden of geven er de voorkeur aan niet over hun problemen te praten.[9] Wat er moet gebeuren na een positieve screening, blijft een onderzoeksvraag op zichzelf.[7]

Bij het bepalen van de ernst van psychische klachten geldt het psychiatrisch interview overigens nog altijd als gouden standaard als het gaat om prognostische waarde, contextuele beoordeling van functionele beperkingen en om behoefteanalyse voor extra psychologische behandeling.[6] Uit een meta-analyse van 94 onderzoeken met bijna 15000 deelnemers in oncologische, hematologische en palliatieve ziekenhuissettings werd geconcludeerd dat 30-40% van de kankerpatiënten last heeft van (een combinatie van) psychiatrische stoornissen.[10]

De gevolgen van psychische klachten bij kanker zijn groot

Het aanpakken van psychische klachten van kankerpatiënten is belangrijk omdat deze klachten ingrijpende gevolgen hebben voor de individuele patiënten voor de samenleving als geheel. Psychologische comorbiditeit bij kanker wordt in verband gebracht met verminderde kwaliteit van leven, verminderde naleving van medische adviezen, langere ziekenhuisopname en toegenomen (oneigenlijk) gezondheidszorggebruik.[11-13] Het bieden van psychosociale zorg aan kankerpatiënten kan op de lange termijn dus leiden tot kostenbesparingen, aangezien kankerpatiënten die baat hebben bij psychosociale zorg minder gebruik maken van andere gezondheidszorgdiensten.[14] Dit fenomeen wordt *cost-offset* genoemd: verhoogd mentaal welbevinden zou moeten leiden tot een verhoogde therapietrouw in de behandeling tegen kanker en veranderingen in levensstijl (bijvoorbeeld stoppen met roken). Bovendien kunnen productiviteitsverliezen bij de werkende kankerpopulatie worden verminderd.[14]

Bewezen effectieve psychologische behandelingen voor kankerpatiënten zijn beschikbaar

Het aantal patiënten met kanker neemt toe in de komende jaren. Dat betekent dat er ook steeds meer mensen met kanker behoefte zullen hebben aan psychologische zorg.

In de afgelopen 30 jaar zijn er gelukkig steeds meer bewezen effectieve, ofwel "evidence based" psychologische behandelingen voor kankerpatiënten beschikbaar geworden. Onderzoek laat kleine tot middelgrote positieve effecten van psycho-oncologische interventies zien op emotionele stress, angst, depressie en gezondheidsgerelateerde kwaliteit van leven (QoL). Deze effecten blijven meestal op middellange en zelfs lange termijn gehandhaafd.[15] Daarnaast lijkt deze zorg een gunstige kosten-batenverhouding te hebben. Een overzicht van 11 kosteneffectiviteitsstudies van psycho-oncologische interventies concludeerde dat psycho-oncologische zorg waarschijnlijk kosteneffectief is, afhankelijk van hoeveel de samenleving bereid is te betalen voor een toename van kwaliteit van leven.[16] Aangezien de mate van psychische klachten het hoogst is bij mensen met kanker op jonge leeftijd [6] die

nog een heel beroepsleven voor zich hebben, is er bovendien een potentieel groot economisch effect van vroege en effectieve psychologische interventies in termen van het verminderen van productiviteitsverlies.

Ondanks bewezen effectiviteit en kosteneffectiviteit zijn evidence-based psychologische behandelingen niet altijd toegankelijk voor kankerpatiënten vanwege stigma, terughoudendheid om weer naar het ziekenhuis of een andere zorginstelling te moeten afreizen en indirecte kosten zoals reis- en tijdinvesteringen.[17] Daarom worden deze interventies steeds vaker via internet aangeboden. Via internet aangeboden interventies zijn gemakkelijk toegankelijk, besparen reistijd en kunnen net zo effectief zijn als hun face-to-face tegenhangers.[18, 19]

Van alle evidence-based psychologische behandelingen in de psycho-oncologie is er het sterkste bewijs voor cognitieve gedragstherapie (CGT) en op mindfulness gebaseerde interventies (MBI's).[20]

Cognitieve gedragstherapie

Cognitieve gedragstherapie (CGT) wordt beschouwd als de gouden standaard voor de behandeling van psychopathologie in het algemeen [21] en bij psychische klachten bij kanker.[20] CGT richt zich op het identificeren en uitdagen van irrationele negatieve automatische gedachten om deze in meer realistische of behulpzame gedachten te veranderen. Het is vervolgens gericht op het veranderen van maladaptief gedrag. [22] Een Cochrane review uit 2015 gericht op psychologische interventies bij niet-gemetastaseerde borstkankerpatiënten waaronder 24 gerandomiseerd gecontroleerde trials (RCT's) naar CGT, liet een aanzienlijke vermindering van angst, depressie en stemmingsstoornissen zien.[23]

Daarnaast neemt het bewijs voor de werkzaamheid van via internet geleverde- CGT bij kankerpatiënten toe. Onbegeleide online CGT werd effectief bevonden in het verminderen van psychische stress en vermoeidheid [24-26] het verbeteren van QoL [25], het verbeteren van emotioneel en sociaal functioneren [26], en zelfredzaamheid. [27]

Op mindfulness gebaseerde interventies

Naast CGT wordt er in de psycho-oncologie onderzoek gedaan naar op mindfulness gebaseerde interventies ("Mindfulness-based interventions", MBI's), zoals Mindfulness-gebaseerde Stress Reduction (MBSR) [28] en Mindfulness-based Cognitive Therapy (MBCT).[29] Mindfulness wordt vaak gedefinieerd als: "Het vermogen om aandacht te geven aan het huidige moment op een speciale manier: in het huidige moment,

open en onderzoekend met vriendelijke interesse en zonder te oordelen".[28] Terwijl CGT zich richt op het identificeren en uitdagen van irrationele gedachten en gedrag, zijn veel kankergerelateerde gedachten en cognities niet irrationeel. Angst voor terugkeer van kanker is alles behalve irrationeel - het kan zelfs motiveren tot positief gezondheidsgedrag en daardoor de kans op terugkeer van kanker verkleinen.[30] In plaats van je te richten op de inhoud van cognities, kan het behulpzamer zijn om je bewust te worden van hoe je je verhoudt tot moeilijke gedachten, emoties of pijnlijke lichamelijke gewaarwordingen.

De beoefening van mindfulness stelt mensen in staat om een radicale verandering te bewerkstelligen in hoe ze zich verhouden tot hun gedachten, gevoelens en lichaamssensaties, evenals hun omstandigheden. Zo kan je de gebruikelijke, geconditioneerde manieren om te reageren, die niet altijd behulpzaam zijn, leren herkennen. Dat stelt je in staat om bewuste keuzes te kunnen maken.[29] MBI's richten zich zodoende op het vergroten van het vermogen om de ondubbelzinnige realiteit van het leven met kanker te omarmen, en het vermogen om vriendelijke aandacht te besteden en vrij en intentioneel te kiezen hoe je omgaat met het omgaan met deze gedachten, emoties en lichamelijke gewaarwordingen, zonder ze kwijt te hoeven raken.

Het bewijs voor de effectiviteit van MBI's in de oncologie is de afgelopen twee decennia snel toegenomen. MBI's hebben gunstige effecten op depressie, angst, angst voor terugkeer van kanker en vermoeidheid.[31] Hoewel de eerste resultaten aangeven dat MBI's kosteneffectief zijn in de kankerzorg [32, 33], zijn de kosteneffectiviteits-beoordelingen van MBI's schaars.[34]

MBI's worden ook via internet aangeboden, maar onderzoek naar internet-MBI's (eMBI's) is vooral gericht op de effectiviteit van eMBI's in algemene (gezonde) populaties. Studies gericht op de effectiviteit van eMBI's bij kankerpatiënten zijn schaars. Eén enkel gecontroleerd onderzoek (*n*=62) toonde de haalbaarheid aan van aangepaste MBSR voor kankerpatiënten via internet.[35] Een ander pilot-onderzoek bevestigde dat MBSR geleverd via een iPad mogelijk haalbaar en acceptabel is voor borstkankerpatiënten.[36] Hoewel MBI's eerder hun potentie als aanvullende psychologische behandeling voor kankerpatiënten hebben aangetoond, is er nooit een goed ontworpen RCT uitgevoerd waarbij zowel internet-MBCT als groeps-MBCT voor kankerpatiënten werd vergeleken met gebruikelijke zorg.

Het BeMind onderzoek – een samenvatting van de bevindingen

In dit proefschrift is daarom onderzoek gedaan naar de effectiviteit en kosteneffectiviteit van Mindfulness-Based Cognitieve Therapie in groepsvorm (MBCT) en MBCT

aangeboden via internet (eMBCT) vergeleken met gebruikelijke zorg ("Treatment as Usual", afgekort als "TAU") in een steekproef van 245 patiënten met kanker die last hadden van psychische klachten.

In hoofdstuk 2 werd de hypothese onderzocht dat psychiatrische stoornissen en psychische klachten geassocieerd zijn met een toename in gebruik en kosten van de gezondheidszorg. De onderzoekspopulatie bestond uit 245 patiënten met op zijn minst milde psychische klachten. Patiënten werden beoordeeld met een gestructureerd psychiatrisch interview voor DSM-IV-TR-as-I-stoornissen op de aanwezigheid van depressieve stoornissen, angststoornissen en/of aanpassingsstoornissen. Psychische stress werd gemeten door de Hospital Anxiety and Depression Scale, een zelfinvulvragenlijst. Retrospectief gebruik van gezondheidszorg in de afgelopen 3 maanden werd verzameld met behulp van de TiC-P, een zelfrapportagevragenlijst die samen met een van de onderzoekers in een interview werd ingevuld. In totaal had 36% van de patiënten een psychiatrische stoornis. Dit hield verband met gebruik en kosten van geestelijke gezondheidszorg en meer gebruik van complementaire zorg. Er werd daarnaast een trend van hoger gebruik van somatische gezondheidszorg bij patiënten met psychiatrische stoornissen geconstateerd. Psychische klachten bleken, in het kort, geassocieerd te zijn met een hoger gebruik van geestelijke gezondheidszorg en kosten.

De BeMind-studie, zoals beschreven in hoofdstuk 3 en 4, betrof een drie-armige multicentre RCT bij 245 patiënten met kanker en met op zijn minst milde psychische klachten die willekeurig werden toegewezen aan MBCT (*n*=77), eMBCT (*n*=90) of TAU (*n*=78). De primaire uitkomst betrof de mate van psychische klachten direct na de behandeling. De mate van voortijdige uitval was significant hoger in de eMBCT dan in de MBCT-groep. Patiënten rapporteerden significant minder psychische klachten na na beide MBCT-interventies vergeleken met TAU. Bovendien was de prevalentie van psychiatrische diagnoses lager in zowel MBCT (33%) als eMBCT (29%) in vergelijking met TAU (16%), maar deze veranderingen waren niet significant. Beide interventies verminderden de angst voor recidief van kanker, rumineren en verbeterden geestelijke gezondheidsgerelateerde kwaliteit van leven, mindfulnessvaardigheden en positieve mentale gezondheid wel significant in vergelijking met TAU. De fysieke gezondheidsgerelateerde kwaliteit van leven verbeterde niet.

Hoofdstuk 5 was gericht op het verkennen van ervaren facilitators en barrières tijdens de eMBCT door zowel patiënten als therapeuten. In totaal namen 31 patiënten deel aan een individueel interview na de behandeling en werden acht therapeuten geïnterviewd in een focusgroepinterview. Er kwamen vier overkoepelende thema's naar voren die grotendeels overeen kwamen tussen patiënten en therapeuten: behandelomgeving,

behandelvorm, rol van de therapeut en patiëntkenmerken. Met betrekking tot de behandeling gaven zowel patiënten als therapeuten aan dat ze veel flexibeler zijn in wanneer, waar en hoe ze zich bezighielden met eMBCT. Zowel patiënten als therapeuten meldden dat ze werden gefaciliteerd door dit gevoel van autonomie in de eMBCT. Patiënten gaven aan dat ze de verhalen van andere patiënten niet hoefden te verwerken. Therapeuten gaven aan dat ze de interventie beter konden afstemmen op individuele thema's. Er waren ook verschillen tussen patiënten en therapeuten. Voor therapeuten leek de eMBCT een grotere tijdsinvestering te vereisen in vergelijking met MBCT. Met betrekking tot de behandelvorm noemden patiënten specifiek de asynchroniciteit als een barrière voor de rol van de therapeut omdat de asynchrone communicatie de dialoog belemmerde. Therapeuten waren meer bezig met het voorkomen van uitval. Ze noemden dat ze door het missen van non-verbale informatie niet in staat werden gesteld om het afhaken van patiënten in een vroeg stadium te herkennen.

Hoofdstuk 6 was gericht op de kosteneffectiviteit van beide MBCT-interventies in vergelijking met TAU. Dit kosteneffectiviteitsonderzoek werd parallel uitgevoerd aan de eerder beschreven RCT. Gezondheidszorgkosten en (informele) werkgerelateerde productiviteitsverlieskosten werden gemeten door middel van interviews. Uitkomsten werden uitgedrukt in termen van Quality Adjusted Life Years (QALY). Een economische evaluatie werd uitgevoerd vanuit een maatschappelijk perspectief met een tijdshorizon van 3 maanden. Betaalde werkgerelateerde productiviteitsverlieskosten en maatschappelijke kosten waren lager in beide MBCT's in vergelijking met TAU. Bovendien verbeterde de kwaliteit van leven in eMBCT en MBCT vergeleken met TAU. De resultaten wijzen uit dat zowel eMBCT als MBCT kostenbesparende behandelingen zijn en tegelijkertijd de kwaliteit van leven verbeteren voor patiënten met kanker en psychische klachten. Een extrapolatie van de onderzoeksgegevens naar een tijdspad van 9 maanden liet daarnaast een vergelijkbaar patroon zien van superioriteit van beide interventies ten opzichte van TAU. Verbeteringen van kwaliteit van leven na 9 maanden follow-up bleven stabiel in beide experimentele interventies vergeleken met de uitkomst na drie maanden.

Discussie

Het onderzoek in dit proefschrift illustreert op een robuuste manier dat MBCT en eMBCT effectieve alternatieven zijn voor gebruikelijke zorg, met minder psychische klachten tot gevolg, minder angst voor terugkeer van kanker, minder rumineren en meer positieve mentale gezondheid en welzijn en een hogere kwaliteit van leven. Bovendien toonde ons kosteneffectiviteitsonderzoek de dominantie van beide interventies in vergelijking

met TAU: MBCT leidt in deze populatie zelfgeselecteerde patiënten met kanker en psychische klachten tot lagere maatschappelijke kosten en een hogere kwaliteit van leven.

De resultaten van de RCT zijn in overeenstemming met meta-analyses van eerdere RCT's op MBI's voor het verminderen van psychische klachten bij kankerpatiënten.[31, 37] Deze effecten bleken meestal stabiel op de middellange en zelfs lange termijn. [15] In het verlengde hiervan toonde de vervolgstudie van het BeMind-project (niet opgenomen in het huidige proefschrift) ook een consolidatie van het behandelresultaat tijdens de follow-upperiode van negen maanden. Interessant is dat de resultaten na verloop van tijd zelfs positiever werden, vooral in eMBCT.[38]

Bovendien laten deze resultaten overtuigend zien dat het internet MBCT veel toegankelijker maakt voor kankerpatiënten zonder extra kosten en zonder de effectiviteit van de interventie in gevaar te brengen. Omdat veel kankerpatiënten obstakels ervaren in het deelnemen aan face-to-face psychologische interventies [17, 39], kan het via internet aanbieden van psychologische interventies bijzonder krachtig zijn in de oncologische context, wanneer patiënten worden gehinderd door fysieke (bijv. reisafstand) of mentale barrières (bijv. niet opnieuw het ziekenhuis willen bezoeken). [40] Het huidige onderzoek draagt in hoge mate bij tot het nauwelijks beschikbare bewijs voor MBI's via internet in de oncologie.

Niettemin gaf ons kwalitatief onderzoek in hoofdstuk 5 wel aan dat er nog veel te verbeteren valt in het ontwerp en de aanbiedingsvorm van eMBCT. Dit impliceert dat technische verbetering noodzakelijk is en dat nieuwe behandelmethoden nader moeten worden onderzocht in toekomstig onderzoek.

De resultaten van onze kosteneffectiviteitsanalyse in hoofdstuk 6 laten zien dat zowel MBCT als eMBCT de potentie hebben om de maatschappelijke kosten al tijdens de interventieperiode te verminderen. Dit is een geweldige prestatie en het is belangrijke informatie, aangezien evaluaties van de kosteneffectiviteit van psychologische behandelingen hard nodig zijn in de psychosociale oncologie.[16] De huidige resultaten zijn gedeeltelijk in overeenstemming met eerdere bevindingen over de kosteneffectiviteit van MBI's voor kankerpatiënten.[32, 33, 41] Het feit dat onze resultaten wijzen op een kostenbesparing na MBCT is hoogstwaarschijnlijk het resultaat van de zelfgeselecteerde aard van de huidige steekproef.

Kortom, onze studie naar MBCT bij kankerpatiënten is de eerste studie die aangeeft dat MBCT, zowel in een groep als via internet, minder psychische klachten en een hogere kwaliteit van leven oplevert, terwijl tegelijkertijd maatschappelijke kosten worden bespaard.

Sterke punten van dit proefschrift

Dit proefschrift bevat de eerste grootschalige RCT van eMBCT en MBCT bij kankerpatiënten in Nederland met behulp van een grote, klinisch representatieve en heterogene steekproef van kankerpatiënten met verschillende tumortypen in verschillende stadia van de ziekte. Dit is een sterk punt, aangezien borstkankerpatiënten tot dusverre oververtegenwoordigd zijn in studies over MBI's bij kankerpatiënten [42] en uitbreiding van de evidence-base van psycho-oncologische interventies in bijvoorbeeld palliatieve populaties noodzakelijk is.[20]

Bovendien hebben we een patiëntgerichte wervingsmethode gebruikt. In de BeMind-studie slaagden we erin meer dan 500 patiënten te werven en 245 patiënten te includeren in een periode van ongeveer 20 maanden. Werven door middel van zelfselectie was snel en effectief.[43]

Bovendien werd deze studie uitgevoerd in verschillende klinische settings, wederom ten voordele van de klinische representativiteit.

Het MBCT protocol is gevolgd in zowel de MBCT als in de eMBCT en onze mindfulness-trainers voldeden aan de criteria van de Vereniging van Mindfulness-Based Trainers in Nederland en Vlaanderen. Bovendien hadden alle betrokken trainers eerdere ervaring met het verlenen van psychologische zorg aan kankerpatiënten.

Beperkingen van dit proefschrift

Naast de sterke punten van het huidige proefschrift, moeten enkele beperkingen worden genoemd. Ons onderzoeksdesign liet niet toe om te bepalen of consolidatie van de behandelingseffecten het gevolg is van de MBCT-interventies of van natuurlijk herstel of regressie naar het gemiddelde (hoewel opgemerkt moet worden dat we deze trend in de gebruikelijke zorg-groep gedurende de drie maanden niet hebben waargenomen).

Daarnaast liet het design niet toe om te bepalen of de nieuwe interventie (eMBCT) slechter presteerde dan de interventie die al ontwikkeld was (MBCT) middels een zogeheten non-inferiority analyse.

MBCT en eMBCT verschilden niet alleen in het online versus face-to-face aspect, maar ook of ze individueel of met groepsgenoten deelnamen. Dit impliceert dat de effecten van verschillende aanbiedingsvormen en die van lotgenotencontact in de huidige studie niet kunnen worden onderscheiden.

Onze RCT bevatte geen actieve maar een gebruikelijke-zorg conditie. De meeste mindfulness-onderzoeken die zijn uitgevoerd in de oncologie hebben wachtlijstcontrolegroepen gebruikt in plaats van actieve interventies.[44] Hoewel dit onderzoeksontwerp passend is in deze fase van onderzoek, hebben toekomstige studies over MBCT op internet meer rigoureuze designs nodig met bijvoorbeeld actieve controlegroepen.[44, 45] Met deze studie kunnen we niet concluderen of MBCT en eMBCT effectiever zijn dan andere evidence-based benaderingen voor psychische klachten bij patiënten met kanker, zoals cognitieve gedragstherapie.

Aanbevelingen voor vervolgonderzoek

Het huidige proefschrift heeft, zoals het een proefschrift betaamt, stof tot nadenken gegegeven. De eMBCT heeft nog niet zijn volledige potentie benut in zijn huidige vorm en moet worden verbeterd om patiëntvriendelijkheid, toegankelijkheid en therapietrouw te waarborgen. Bovendien was de eMBCT in zijn huidige vorm redelijk bewerkelijk. Andere vormen van eMBCT zouden moeten worden onderzocht om de therapietrouw en mogelijkheid tot schaalvergroting van de interventies te verbeteren. In het verlengde daarvan dringen we er bij relevante partijen, zoals zorgverzekeraars, op aan om financiële ondersteuning te bieden voor de doorontwikkeling van e-healthinterventies.

We stellen ons twee aangepaste eMBCT-vormen voor. Ten eerste lijkt het interessant om face-to-face groep-MBCT-sessies te combineren met extra internetsessies in een zogeheten blended-MBCT. Ten tweede geven veel patiënten met kanker de voorkeur aan zelfhulp.[9, 17] Daarom moeten de mogelijkheden van onbegeleide MBCT-interventies worden onderzocht. Zelfhulpinterventies zijn makkelijk op grote schaal aan te bieden tegen minimale kosten. Samen omvatten deze interventies de ontwikkeling van een op mindfulness gebaseerd stepped-care-programma met verschillende niveaus van MBCT-intensiteit overeenkomstig met de verschillende behoeften en voorkeuren van verschillende patiënten.

Verder hebben we ook meer onderzoek nodig naar de langetermijnresultaten van de follow-up. Lange-termijn follow-up vergelijkingen ontbreken vaak in onderzoek naar internet- interventies. Interessant genoeg leken patiënten meer baat te hebben

bij eMBCT dan MBCT op langere termijn. Toekomstige RCT's zouden bij voorkeur een langere vergelijkingscontrolegroep moeten bevatten om de resultaten op de lange termijn voor de te bepalen.

Om te kunnen voorspellen welke behandeling (internet- of groeps-MBCT) het beste werkt voor wie, moet toekomstig onderzoek daarnaast ook meer licht schijnen op predictoren en moderatoren van het interventie-effect in MBCT.[46] Daarnaast moeten we kijken naar mediërende variabelen om onderliggende processen te vangen die verantwoordelijk zijn voor therapeutische verandering.[47, 48]

Klinische implicaties

De bevindingen in dit proefschrift leiden tot een aantal aanbevelingen voor de klinische praktijk. Ten eerste zouden we er verstandig aan doen om MBCT voor patiënten met kanker en psychische klachten te vergoeden. Hoewel MBCT voor patiënten met kanker en psychische klachten effectief is en geld bespaart, adviseert het college van Zorgverzekeringen aan de minister om MBCT alleen te vergoeden voor patiënten met een psychiatrische stoornis. Aangezien slechts een minderheid van patiënten met kanker voldoet aan de diagnostische criteria voor een psychiatrische stoornis, kan MBCT lang niet aan alle patiënten met kanker worden aangeboden. Dit creëert ongelijkheid tussen patiënten die de behandeling kunnen betalen en diegenen die het niet kunnen betalen.

Daarnaast moeten we ons inspannen om MBCT te implementeren in de dagdagelijkse klinische praktijk. Zoals Greer in 1994 al zei: "De meest urgente taak van psycho-oncologie is het dichten van de gapende kloof tussen huidige kennis en klinische zorg in de praktijk".[49]

Bovendien betekent de implementatie van eMBIs in de klinische praktijk dat de pool van trainers moet worden vergroot en dat meer online MBI-therapeuten moeten worden opgeleid. Maar wat betekent het om een goede online mindfulness-trainer te zijn? Er is geen standaard beschikbaar voor het bepalen van de kwaliteit van online trainers. Trainingsmethoden zullen moeten worden ontwikkeld om bekwame online mindfulness-trainers op te leiden.

Conclusie

Samenvattend biedt dit proefschrift overtuigend bewijs voor de effectiviteit van zowel individuele MBCT via internet als voor MBCT in groepsvorm voor patiënten met kanker die last hebben van psychische klachten. Tegelijkertijd genereerde dit proefschrift ook belangrijke vragen voor vervolgonderzoek. Hopelijk moedigen deze resultaten andere

onderzoekers aan om het onderzoek naar MBCT voor patiënten met kanker, voort te zetten, om zo een optimale vorm van MBCT voor de groep patiënten met kanker te ontwikkelen. Daar waar patiënten behoeftes hebben die verder reiken dan gangbare psychologische interventies zoals cognitieve gedragstherapie, kan MBCT een optie zijn. Voor de steeds groter wordende groep patiënten met kanker, waarvan een aanzienlijke minderheid psychische klachten heeft, is MBCT in ieder geval een belangrijke effectieve én kosteneffectieve aanvulling op het bestaande psychologische behandelaanbod.

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DANKWOORD

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Angela, wat hebben we het goed samen. Ik vind het heel fijn om samen met jou door het leven mogen te gaan. Samen kunnen we genieten van burgerlijke kneuterigheid maar we maken ook grootse plannen. Je brengt heel veel humor, frisheid en plezier in mijn leven. Ik ben gek op jou en kijk heel erg uit naar nog heel vaak wakker worden naast jouw guitige lachje.

PHD PORTFOLIO

Activities		Hours
Supervisor Master Thesis students Gezondheidszorgpsychologie		50
Tutor Cancer Research 5DIF1		30
Trainer Mindfulness-based Stress Reduction		108
Supervisor Research Internship HAN Toegepaste Psychologie		50
Member Gammaraad psychosociale oncologie		30
Attendee and presenter Grand Round Radboudumc Psychiatrie		60
Journal Club psychosociale oncologie		60
Tutor Mindfulness for (bio)medical professionals		90
Reviewer for journals Journal of Supportive Care in Cancer, BMC Cancer, Trials, Palliative Medicine, Psycho-Oncology, JMIR, Behaviour Research and Therapy,		30
Redactielid Tijdschrift Nederlandse Vereniging Psychosociale Oncologie		60
Member research meetings / journal club Centre for Mindfulness		60
Netherlands Society for Research on Internet Interventions congress 2013	10-11-2013	8
Vereniging Gedragstherapie en Cognitieve Therapie najaarscongres 2013	15-11-2013	8
Landelijk Mindfulness Symposium 2014	22-5-2014	8
Presentation "Mindfulness in medicine" at Zorginstituut Nederland	2-12-2015	4
Open Huis Centrum voor Mindfulness 2015	15-9-2015	8
Landelijk Mindfulness Symposium 2016	21-5-2016	8
International Congress on Behavioural Medicine 2016 Melbourne	12-10-2016	32
Loopbaanmanagement voor promovendi	2-1-2017	20
International Psycho-Oncology Society congress 2017 Berlin	16-8-2017	24
Verenging cognitieve gedragstherapie najaarscongres 2017	11-9-2017	8
International Conference on Mindfulness 2018 Amsterdam	13-7-2018	24
NVvP voorjaarscongres Maastricht 2019	4-3-2019	4

Courses		ECTS
Management voor Promovendi	2-1-2014	3
RIHS introduction course	25-3-2014	1.8
Presentation Skills	3-1-2015	1.5
Opfriscursus statistiek voor promovendi	11-1-2015	1.5
Psychodiagnostiek MPSGP14a	2-2-2016	8

Courses		ECTS
Wetenschapsjournalistiek	4-1-2016	3
NIHES CE08 Repeated Measurements	22-4-2016	1.7
Donders PhD intro meeting for RIHS switchers	9-12-2016	0.3
Post-academische opleiding tot mindfulness trainer	30-6-2017	
Basiscursus Regelgeving en Organisatie voor Klinisch onderzoekers (BROK)	6-5-2018	1.8
Psychopathologie MPSGP12	11-5-2018	8
Psychologische Interventies MPSGP11	29-1-2019	8
Vaardigheidstraining Neuropsychologische Revalidatie MPSGP13d	2-1-2019	3
Vaardigheidstraining Klachtgerichte Interventies MPSGP13c	2-1-2019	3

CURRICULUM VITAE

Félix Compen was born in Besançon (France) on August 24th, 1989. He finished his secondary education at the Isendoorn College in Warnsveld in 2007. He moved to Nijmegen to study Psychology at the Radboud University Nijmegen. In 2013, he obtained his Research Master's degree cum laude and he subsequently started his PhD project at the Department of Psychiatry, Radboud University Medical Centre. In collaboration with the Helen Dowling Institute and together with his colleague Else Bisseling he has conducted a randomized controlled trial which led to the current dissertation. In addition to his PhD project, Félix has successfully completed the two-year mindfulness teacher training at the Radboudumc Centre for Mindfulness, department of Psychiatry. After obtaining his PhD, will start his training to become a licensed psychologist ("GZ-psycholoog") at the Radboudumc, department of Psychiatry. Félix lives happily together with his girlfriend Angela in Arnhem.

LIST OF PUBLICATIONS

1. **Compen FR**, Bisseling EM, Van der Lee ML, Adang EM, Donders ART, Speckens AEM, *Study protocol of a multicenter randomized controlled trial comparing the effectiveness of group and individual internet-based Mindfulness-Based Cognitive Therapy with treatment as usual in reducing psychological distress in cancer patients: the BeMind study.* BMC Psychology, 2015. **3**: p. 27.

2. **Compen FR**, Bisseling EM, Schellekens MP, Jansen ET, van der Lee ML, Speckens AE, Mindfulness-Based Cognitive Therapy for Cancer Patients Delivered via Internet: Qualitative Study of Patient and Therapist Barriers and Facilitators. Journal of Medical Internet Research, 2017. **19**(12): p. e407.

3. **Compen F**, Adang E, Bisseling E, Van der Lee M, Speckens A, *Exploring associations between psychiatric disorder, psychological distress, and health care utilization in cancer patients.* Psycho-Oncology, 2018. **27**(3): p. 871-878.

4. **Compen F**, Bisseling E, Schellekens M, Donders R, Carlson L, Van der Lee, M, Speckens A, *Face-to-Face and Internet-Based Mindfulness-Based Cognitive Therapy Compared With Treatment as Usual in Reducing Psychological Distress in Patients With Cancer: A Multicenter Randomized Controlled Trial.* Journal of Clinical Oncology, 2018. **36**(23): p. 2413-2421.

5. **Compen FR**, Adang EMM, Bisseling EM, Van der Lee ML, Speckens AEM, *Cost-effectiveness of individual internet-based and face-to-face Mindfulness-Based Cognitive Therapy compared to Treatment As Usual in reducing psychological distress in cancer patients.* Revised and resubmitted.

Not included in this thesis:

6. Thewes B, Rietjens JAC, van den Berg SW, **Compen FR**, Abrahams H, Poort H, van de Wal M, Schellekens MPJ, Peters M, Speckens AEM, Knoop H, Prins JB, *One way or another: The opportunities and pitfalls of self-referral and consecutive sampling as recruitment strategies for psycho-oncology intervention trials.* Psycho-Oncology, 2018. **27**(8): p. 2056-2059.

7. Cillessen L, Schellekens MPJ, Van de Ven MOM, Donders ART, **Compen FR**, Bisseling EM, Van der Lee ML, Speckens AEM, *Consolidation and prediction of long-term treatment effect of group and online mindfulness-based cognitive therapy for distressed cancer patients.* Acta Oncologica, 2018. **57**(10): p. 1293-1302.

8. Bisseling EM, Schellekens MPJ, Spinhoven P, **Compen FR**, Speckens AEM, van der Lee ML, *Therapeutic alliance—not therapist competence or group cohesion—contributes to reduction of psychological distress in group-based mindfulness-based cognitive therapy for cancer patients.* Clinical Psychology & Psychotherapy, 2019: doi: 10.1002/cpp.2352.[Epub ahead of print].

DATA MANAGEMENT STATEMENT

This thesis is based on the results of human studies, which were conducted in accordance with the principles of the Declaration of Helsinki. The medical and ethical review board Committee on Research Involving Human Subjects Region Arnhem Nijmegen, Nijmegen, The Netherlands has given approval to conduct these studies (CMO Arnhem – Nijmegen 2013/542).

This project is stored on the Radboudumc, department server: (H:)PSYdata$ in the folder: H:\Research\BeMind. The patient data for the analyses of the studies as presented in chapter 2, 4, 5, and 6 is stored on this departments' H-drive in a secured folder specifically for this project to which access is only granted to authorized personnel, as to be determined by the management of the department of Psychiatry.

All paper informed consent forms are stored in a locked cabinet at the Centre for Mindfulness. Data management and monitoring were performed using a Microsoft Excel file which is also stored in the secured folder on the department server. An audit trail was incorporated to provide evidence of the activities that has altered the original data. The privacy of the participants in this study is warranted by use of encrypted and unique individual subject codes. This code correspondents with the code used in the patient report forms. The code was stored separately from the study data in a separate folder on the department server. Patient report forms were converged from Surveymonkey to SPSS (SPSS Inc., Chicago, Illinois, USA). The original Surveymonkey files are also available.

The data will be saved for 15 years after termination of the study (December 21, 2015). Using these patient data in future research is only possible after a renewed permission by the patient as recorded in the informed consent. The datasets analyzed during these studies are available from the corresponding author on reasonable request.

DONDERS GRADUATE SCHOOL FOR COGNITIVE NEUROSCIENCE

For a successful research Institute, it is vital to train the next generation of young scientists. To achieve this goal, the Donders Institute for Brain, Cognition and Behaviour established the Donders Graduate School for Cognitive Neuroscience (DGCN), which was officially recognised as a national graduate school in 2009. The Graduate School covers training at both Master's and PhD level and provides an excellent educational context fully aligned with the research programme of the Donders Institute.

The school successfully attracts highly talented national and international students in biology, physics, psycholinguistics, psychology, behavioral science, medicine and related disciplines. Selective admission and assessment centers guarantee the enrolment of the best and most motivated students.

The DGCN tracks the career of PhD graduates carefully. More than 50% of PhD alumni show a continuation in academia with postdoc positions at top institutes worldwide, e.g. Stanford University, University of Oxford, University of Cambridge, UCL London, MPI Leipzig, Hanyang University in South Korea, NTNU Norway, University of Illinois, North Western University, Northeastern University in Boston, ETH Zürich, University of Vienna etc..

Positions outside academia spread among the following sectors: specialists in a medical environment, mainly in genetics, geriatrics, psychiatry and neurology. Specialists in a psychological environment, e.g. as specialist in neuropsychology, psychological diagnostics or therapy. Positions in higher education as coordinators or lecturers. A smaller percentage enters business as research consultants, analysts or head of research and development. Fewer graduates stay in a research environment as lab coordinators, technical support or policy advisors. Upcoming possibilities are positions in the IT sector and management position in pharmaceutical industry. In general, the PhDs graduates almost invariably continue with high-quality positions that play an important role in our knowledge economy.

For more information on the DGCN as well as past and upcoming defenses please visit:

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